SEP 1985

Devices and Technology Branch Contractors Meeting 1984

Summary and Abstracts

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health
National Heart, Lung,
and Blood Institute

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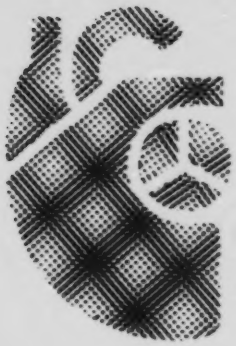

Devices and Technology Branch Contractors Meeting 1984

Summary and Abstracts

Division of Heart and
Vascular Diseases
National Heart, Lung, and
Blood Institute

December 5, 6 and 7, 1984

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health
August 1985

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Meeting Schedule Overview

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DEVICES AND TECHNOLOGY BRANCH CONTRACTORS MEETING
HOLIDAY INN CROWNE PLAZA HOTEL
ROCKVILLE, MARYLAND

December 5-7, 1984

AGENDA

Tuesday, December 4, 1984

6:00 - 9:00 p.m.	Registration Desk Open
6:00 - 8:00 p.m.	Social Hour

****

POSTERS AND DISPLAYS

Ventricular Assist Systems on display in the Regency Room, Wednesday and Thursday. Primary Reference Materials on display in the Regency Room, Wednesday.

****

THE HASTINGS LECTURE WILL BE PRESENTED AT 10:00 A.M., THURSDAY

****

Wednesday, December 5, 1984

7:15 a.m.	Registration
	PLENARY SESSION
7:45 a.m.	Devices and Technology Branch Program Review Dr. John T. Watson
8:00 a.m.	NHLBI Research Training and Development Dr. Donald MacCanon

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Wednesday, December 5, 1984 (continued)

BIOMATERIALS SESSION

Chairpersons: Dr. Sumner Barenberg
Dr. John Sharefkin

Calcification of Prosthetic Materials Program

8:15 a.m. Prosthetic Materials in the Cardiovascular System
Dr. Walter E. Brown

8:30 a.m. Calcification Mechanisms in Cardiovascular Prostheses
Dr. James W. Buchanan

8:45 a.m. Quantification of Regional Platelet Thrombosis and Regional Calcium Mapping on Pericardial Tissue Valve Prostheses With Diphosphonate Treatment
Dr. Mrinal K. Dewanjee

9:00 a.m. Structural Proteins in Bioprosthetic Valve Calcification
Dr. Robert J. Levy

9:15 a.m. Mechanical Etiology of Calcification
Dr. Param Singh

9:30 a.m. Considerations in Deposition and Degradation of Calcified Deposits in Cardiac Assist Devices
Dr. Jane Lian

9:45 a.m. Coffee Break

10:15 a.m. Guest Speaker: Dr. H. Clarke Anderson
Chairman, Department of Pathology
University of Kansas
"Role of Membranes in Skeletal Calcification"

Small Diameter Vascular Grafts Program

10:45 a.m. Endothelial Seeding of Small Vessel Prostheses
Dr. Allan D. Callow

11:00 a.m. Endothelial Seeding of Vascular Grafts
Dr. John Glover and Dr. Malcolm Herring

11:15 a.m. Effects of Compliance Mismatch in Arterial Grafts
Dr. William A. Abbott

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Wednesday, December 5, 1984 (continued)

11:30 a.m.	Application of Arterial Regeneration Dr. Howard P. Greisler
11:45 a.m.	Endothelialization of Detergent-Extracted Canine Vascular Matrix Dr. Klaus Brendel and Dr. Raymond C. Duhamel
12:15 p.m.	LUNCHEON Guest Speaker: Ms. Karen Ramberg Assistant Professor of Radiology Tufts University Medical School "Where Are the Platelets?"

*BIOMATERIALS SESSION

2:30 p.m.	Graft Thrombus Formation and Therapeutic Thrombolysis Dr. Stephen R. Hanson
2:45 p.m.	Bioresorbable Vascular Grafts Dr. Pierre M. Galletti
3:00 p.m.	Surface Structure and Surface Biological Interactions of Polyether Urethanes Dr. Buddy D. Ratner
3:15 p.m.	Chairpersons' Summaries

*ENERGY TRANSMISSION SYSTEMS SESSION

Chairpersons: Dr. Edwin Alderman
Dr. Lee Baker
Dr. Hynda Kleinman

2:30 p.m.	Research and Development of Systems for Transmitting Energy Through Intact Skin Mr. Craig Sherman
2:45 p.m.	Electrical Energy Transmission Through Intact Skin Mr. David H. LaForge

*SIMULTANEOUS SESSIONS

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Wednesday, December 5, 1984 (continued)

ENERGY TRANSMISSION SYSTEMS SESSION (continued)

3:00 p.m. — Development of a Percutaneous Energy Transmission System
Mr. Paul Freed

3:15 p.m. — Development of a Percutaneous Energy Transmission System
Dr. Benedict Daly

3:30 p.m. — Coffee/Cookie Break

Biomaterials/Reference Materials Program

4:00 p.m. — Panel on NHLBI Reference Materials
Moderator: Dr. Suzanne G. Eskin

The Biocompatibility of NHLBI Reference Materials
Dr. James M. Anderson

Panel Members: Dr. Robert I. Leininger
Dr. Sumner Barenberg
Dr. Buddy D. Ratner
Dr. Paul Didisheim

5:15 p.m. — Adjourn

6:00 - 8:00 p.m. — Social Hour

Thursday, December 6, 1984

MECHANICAL CIRCULATORY SUPPORT SESSION

Chairpersons: Dr. Edwin Alderman
Dr. Lee Baker
Dr. Hynda Kleinman

Thermal Energy Ventricular Assist Systems Program

8:30 a.m. — Development of a Thermal Ventricular Assist System
Mr. Maurice White

8:50 a.m. — Development and Evaluation of a Thermocompressor-Powered Thermal Energy System
Dr. A. L. Blubaugh

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Thursday, December 6, 1984 (continued)

9:10 a.m.	Small Business Innovation Research (SBIR) Program Ms. Lily Engstrom SBIR Program Coordinator, NIH
9:40 a.m.	Coffee Break
10:00 a.m.	HASTINGS LECTURE Dr. John C. Norman Cardiac Surgery Beth Israel Medical Center "The Hastings File: A Search for Solutions"
	Electrical Energy Ventricular Assist Systems Program
11:00 a.m.	Development of an Implantable, Integrated Electrically Actuated Left Heart Assist System Mr. Stephen R. Igo
11:20 a.m.	Development of an Implantable Integrated Electrically Powered Left Heart Assist System Dr. David Gernes
11:40 a.m.	Electrohydraulic Left Heart Assist System Dr. Robert Kung
12:15 p.m.	LUNCHEON Guest Speaker: Dr. Larry W. Stephenson Associate Professor of Surgery School of Medicine, University of Pennsylvania "Myocardial Augmentation Using Skeletal Muscle"
2:00 p.m.	Development of an Electrohydraulic-Driven Left Heart Assist System Mr. Kenneth Butler
2:20 p.m.	Development of an Implantable Left Heart Assist System Dr. Peer Portner
2:40 p.m.	DISCUSSION

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Thursday, December 6, 1984 (continued)

2:50 p.m.	PANEL: PHYSIOLOGY AND PATHOPHYSIOLOGY OF CIRCULATORY SUPPORT DEVICES
	Moderator: Dr. John T. Watson
	Panel Members: Dr. William A. Smith Dr. Peer M. Portner Dr. J. Donald Hill Dr. D. Glenn Pennington Dr. Allen K. Ream Dr. Donald B. Olsen Dr. O. Howard Frazier
4:00 p.m.	Coffee/Cookie Break
4:15 p.m.	PANEL: DEVICE READINESS TESTING OF ELECTRICALLY POWERED VAS
	Moderator: Dr. Frank Altieri
	Panel Members: Dr. William Bernhard Mr. Kenneth Butler Dr. Robert Kung Mr. Craig Sherman Mr. Michael Daniel
4:45 p.m.	Chairpersons' Summaries of VAS and Energy Transmission Sessions
5:15 p.m.	Adjourn
6:00 - 8:00 p.m.	Social Hour

Friday, December 7, 1984

DIAGNOSTIC INSTRUMENTATION SESSION

8:15 a.m.	Devices and Technology Branch Program Overview Dr. John T. Watson
8:30 a.m.	Ultrasound B-Scan Assessment Program
	Moderator: Dr. Alan Berson

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Friday, December 7, 1984 (continued)

Panel Members: Dr. James Toole, Chairman
Dr. Gene Bond
Dr. Fred Bryan
Dr. Barry Goldberg
Dr. Daniel O'Leary
Dr. Jeff Raines
Dr. John Ricotta

Presentations: Drs. Raines, Ricotta, O'Leary, and Bond

10:00 a.m. Coffee Break

Image Enhancement of Coronary Arteries Program

Chairpersons: Dr. James Bailey
Dr. Robert Kruger

10:30 a.m. Computer Enhancement of Intravenous Coronary Angiograms
Mr. Robert Selzer

10:45 a.m. Temporal Filtration Fluoroscopy/Tomography/3-D
Dr. James Nelson

11:00 a.m. Image Processing of Coronary Arteriograms
Dr. Maryl Johnson

11:15 a.m. Visualization of Coronary Arteries and Bypass Grafts
Dr. Gabor Herman

Detection and Quantification of Lesions in Deep-Lying Arteries and in Coronary Arteries Program

Chairpersons: Dr. James Bailey
Dr. Robert Kruger

11:30 a.m. Ultrasound System for Detection and Quantification of Lesions in Animals
Dr. Ralph Barnes

11:45 a.m. Noninvasive Detection and Quantification of Atherosclerotic Lesions--NMR Methods
Dr. Leon Kaufman

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Friday, December 7, 1984 (continued)

12:00 p.m.	LUNCHEON Guest Speaker: Dr. William Long Research Associate Laboratory for Computer Science Massachusetts Institute of Technology "Artificial Intelligence Techniques Applied to the Cardiovascular System"
	Detection and Quantification of Lesions in Deep-Lying Arteries and in Coronary Arteries Program (continued)
1:30 p.m.	Digital Coronary Angiography Dr. Martin Kaplitt
1:45 p.m.	Minimally Invasive System for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries Dr. Barrie Hughes
2:00 p.m.	Minimally Invasive System for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries Dr. Erik Ritman
2:15 p.m.	Minimally Invasive System for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries Dr. Donald Sashin
2:30 p.m.	Minimally Invasive System for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries Dr. Theron Ovitt
2:45 p.m.	Minimally Invasive System for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries Dr. Charles Mistretta
3:00 p.m.	Minimally Invasive System for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries Dr. Albert Macovski

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Friday, December 7, 1984 (continued)

3:15 p.m.	Chairpersons' Summaries
3:30 p.m.	Closing Remarks Dr. John T. Watson
	Adjourn

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Eighth Annual Hastings Lecture

John C. Norman, M.D.
Newark Beth Israel Medical Center
Newark, New Jersey

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THE HASTINGS FILE: A SEARCH FOR SOLUTIONS

INTRODUCTION

Good morning, ladies and gentlemen. I am pleased and proud to have been given the opportunity to speak to you on the occasion of this Eighth Annual Hastings Lectureship. I must, however, indicate early on that this opportunity presented to me yet another dilemma. Obviously there were (and are) a multiplicity of approaches to a problem of this type. Many of these have been recorded by some of my distinguished predecessors (table 1).

A careful review of each of these lectures (available from the Program Office)* is an excellent long evening's reading. Each of the previous lecturers has used this occasion to record, briefly, his relationships with Frank Hastings and then to set down, sometimes at considerable length, his views on topics of his choice. In 1977, the eclectic and awesome Arthur Kantrowitz, former chief executive officer of AVCO/Everett Research Laboratory in Massachusetts and now professor at the Thayer School of Engineering at Dartmouth, who designed the reentry nose cone of the Redstone missile and collaborated brilliantly with his brother, Adrian, in the original conception of diastolic augmentation, discussed progress, challenges, gains, and goals of the Artificial Heart Program. In 1978, Theodore Cooper, the brilliant surgical physiologist who headed NHLBI for a decade before leaving to become dean of Cornell Medical School, discussed advocacy, communication, embattlement, and the uncertainty of the Artificial Heart Program. In 1979, the peerless and pioneering Pierre Galletti, whose original and definitive work on heart-lung bypass, membrane oxygenation, and biomaterials established new disciplines, discussed the history and technologic impact of organ replacement endeavors and questioned only whether the clinical artificial heart would be an export or import. In 1980, Fred Huffman, the enviable and incomparable high energy physicist with whom I argued (he was always right) and collaborated for more than a decade in all aspects of implantable nuclear fuel sources coupled to implantable tidal regenerator engines for artificial hearts, discussed antitechnology, Alexis Carrel, and the Neo-Luddite view of technologic progress. In 1981, Grant(ley) LaFarge, the gifted, flawlessly superb clinical and investigative cardiologist, who, along with William Bernhard (of equal superlatives) and our group, brought rigorous, reproducible hemodynamics and cardiovascular physiology to the Program, discussed accountability, basic and applied science in regard to these efforts, and health/care responsibilities. In 1982, Robert Levy, the international expert in lipid transport, kinetics, and metabolism, who succeeded Ted Cooper at the helm of NHLBI and advocated and evaluated the Artificial Heart Program

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*Devices and Technology Branch, Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute, National Institutes of Health Federal Building, Room 31?, Bethesda, Maryland 20205 (301) 496-1586.

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THE HASTINGS LECTURES:

1.	1977	Arthur Kantrowitz "The Artificial Heart in the Time of Timidity" Hanover, New Hampshire (603) 643-3639	Progress Challenges Gains Goals
2.	1978	Theodore Cooper, M.D., Ph.D. "The Artificial Heart Program" Kalamazoo, Michigan (616) 323-7094	Uncertainty Embattlement Advocacy Communication
3.	1979	Pierre M. Galletti, M.D., Ph.D. "Organ Replacement Technology: Its Impact on the Quality and Cost of Medical Care" Providence, Rhode Island (401) 863-3313	History Technologic impact Artificial heart, export or import?
4.	1980	Fred N. Huffan, Ph.D. "Man, the Unknown. Alexis Carrel, 1935" Waltham, Massachusetts (617) 890-8700	Productivity Antitechnology Neo-Luddites
5.	1981	C. Grant LaFarge, M.D. "Accountabilities in the Development of Mechanical Hearts" Santa Fe, New Mexico (505) 988-5196	Accountability Basic and applied science Health/care responsibilities
6.	1982	Robert I. Levy, M.D. "The Artificial Heart Program in a Time of Austerity" New York, New York (212) 694-4138	NHLBI research direction and funding
7.	1983	William P. Murphy, Jr., M.D. "The Changing Research Alliance" Miami, Florida (305) 327-7621	Fiscal support of research: industry/academe

for nearly a decade before becoming dean of the Medical School at Tufts and subsequently vice president of medical affairs at Columbia, discussed NHLBI research direction and funding. Last year, William Murphy, chief executive officer of Cordis Corporation (sales in fiscal 1984 greater than 200 million), the then struggling industrialist son of a Nobel laureate, who first met Frank Hastings at the 1961 ASAIO meeting in Atlantic City after delivering his paper on a program for an arterial pump and had the foresight and vision to conceive of and produce technologic advances for diagnosing and treating cardiovascular diseases, discussed the fiscal support of research and the responsibilities of industry, academe, and the private sector.

All of these previous lecturers used experience, expertise, knowledge, depth, perception, style and eloquence in preparing previous lectures. What then is left to say . . . to write . . . to record? This was my dilemma.

MY SEARCH FOR A SOLUTION

Like all here today, my approach, initially, was to define the magnitude of the problem, i.e., the Eighth Annual Hastings Lecture. At this phase of preparation(s), I was not startled to realize just what participation in the program for two decades has taught me. For example, the 16 categories outlined in figure 1 were purloined from a personal algorithm and used to formulate a plan.

In our laboratories at the Texas Heart Institute is a poster I purchased a decade or more ago at the Harvard Cooperative, during the phase of transferring our activities from Boston to Houston, i.e.,

"Not to decide is to decide,"
Harvey Cox
Dean of Harvard Divinity School, 19/1

My decision, then, was and is (today) to talk to you about Frank Hastings himself, his origins, his background, his approaches, his associates, his concerns, his legacy, his impact, his vision, his tenacity, his patience, his perseverance, and his philosophies. Moreover, I wish to speak to you as I imagine he would, if he were here, as well he should be. And, as we will see, he is very much here. Further, I intend to develop, with you, a philosophy of science drawn from my interaction with Frank and the Program Office. And finally, I would like to look to the future. This lecture, then, could with equal facility be entitled Frank Hastings: Genealogy, Odyssey, and Anthology . . . or His Search for Solutions . . . or To See Clearly and Understand Completely . . . or the Scientific Method, Romanticized vis-a-vis the Artificial Heart Program . . . or Random Recollections of a Remarkable Quaker, etc., etc. In any event, bear with me as I speak for Frank. Consider this a conversation and consider me as his surrogate, by default. And consider

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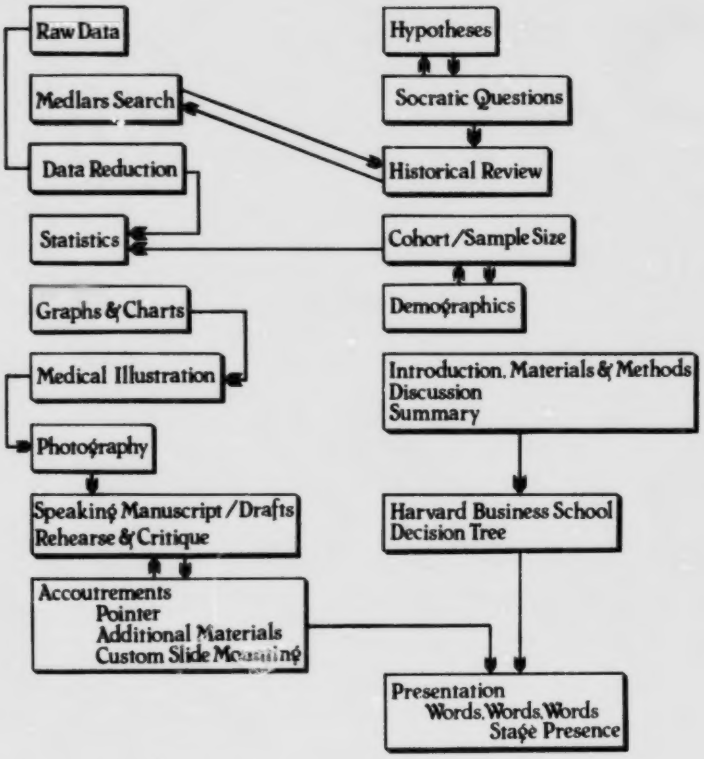

Figure 1--Algorithm used to formulate the Hastings Lecture.

our conversation tentatively entitled "The Hastings File: A Search for Solutions."

"A boy's will is the wind's will,
And the thoughts of youth are long, long thoughts."
Longfellow, "My Lost Youth," 1858

It has been said that we are no more (or less) than that with which we arrive and that to which we are exposed. I first met a member of Frank Hastings' family when I was 19 and his (third) cousin (A. Baird Hastings, professor and chairman of the department) taught me first-year biochemistry at Harvard Medical School and personally introduced me to the intricacies and applicabilities of the Van Slyke apparatus. Meeting Frank directly some 14 years later may have been predictable. For whatever reasons, let us trace our remarkable subject a bit farther back . . . . In so doing, we may better appreciate the origins of some of those attributes that have much to recommend to the participants in the artificial heart arena in 1984, and in years to come . . . for we have only just begun.

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I submit that were he here, Frank Hastings would be somewhat embarrassed by some of the ensuing analogies, aphorisms, syllogisms, dissections and discourses; quietly, and privately, he might be pleased and would certainly agree that our future is bright. Disappointments, frustrations, short-falls, overruns, and somewhat less-than-constructive criticisms were his (and our) legacy and are to be expected. However, lest I stray too far from our central theme, let us return to our analysis. Let me pose some initial Socratic questions. Where did Frank Hastings learn patience? Who taught Frank Hastings perseverance? Why did he value creativity, innovation, precision, rigor, clarity of thought (and action)? I further submit that he probably represented the embodiment of all of these reasonably rare characteristics because of his heritage.

The Hastings File

At the risk of minor time warping, let us open the Hastings File and look back a relatively short 300 years to review 10 generations of Hastings in this country. In 1681, William Penn granted John Hastings (Frank's great, great, great, great grandfather) a Quaker Charter in Philadelphia. The family flourished and moved to the wilds of New Jersey in 1771 to escape the war-like atmosphere of Philadelphia. Eight years later in 1779, the Hastings moved to North Carolina. When Frank's great-grandfather died there in 1859, his great-grandmother (Jane Reese Hastings) moved with her three sons to Indiana, defied jingoism, befriended "hostile" Indians and took them into her home.

Her sons attended Earlham College, and all three became physicians. Frank's grandfather, (the eldest of these three sons) was the physician/innovator and an ardent pacifist. When his younger, married brother was drafted during the Civil War, Frank's grandfather planned to take his place, go to the front, and refuse to fight. He was always a little disgruntled that Abraham Lincoln declared that Quakers could be conscientious objectors before he could make his protest. Further insight into the Hastings heritage can be had by reviewing Frank's grandfather's article entitled "The Part Education Should Play in Providing for a Warless World and International Justice," written in the 1920's when Frank's grandfather was over 80 years of age. His son (Frank's father) was also a physician and director of research at the Quaker/Cancer Jean's Hospital in Philadelphia. Frank (1919-1971) is our subject, and two of his three sons (Larry, recently of Salt Lake and shown here at the console of the Kolff/DeVries/Jarvik/Olsen Clinical Artificial Heart and currently at the Humana Heart Institute in Louisville, and David, the Ph.D. physiologist, of the University of South Dakota School of Medicine) are here with us today.

One can reasonably conclude, then, that what could be construed as extraordinary . . . was (and is) in actuality quite ordinary when viewed by Hastings standards. By this, I only wish to submit that Hastings have been blessed for 10 generations with extraordinary service, with extraordinary capacity, with extraordinary vision, with extraordinary

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circumstance, and with extraordinary contributions. Only Frank, his family, and his forebears would consider their contributions to be ordinary. We who were fortunate to have known and worked with Frank Hastings knew, from the outset, that we had much to learn from him and his Artificial Heart Program.

Next, I would like to examine more closely, to focus, if you will, to magnify and scan for you . . . Frank Hastings and record some less well-known facts. Frank was born January 8, 1919, in Chicago, the only son of Dr. Willard Seth and Faith Olmstead Hastings. His older and younger sisters (Mrs. Doris Darnell, now of Philadelphia, and Mrs. Shirley Hastings Glassco of Lafayette, California, recall that he did not talk openly until the age of four . . . having developed a private language that allowed communication with others at will. Four decades later, we who were directed, interrogated, and inspired by him were probably exposed to the vestiges of this talent of professional listening. In the first grade, it became apparent that he had decreased visual acuity. In order not to be embarrassed, each night he apparently memorized each page, each illustration, and what others had said. Finally, someone covered the illustrations and uncovered his disability (astigmatism and myopia). By this time, however, his input trade-offs had developed keenly and he prevailed; the patterns of ingenuity, coupled with near-total recall, were set. At 15, Frank entered the Westtown Preparatory School and subsequently applied to Haverford College. He was nearly not accepted (figure 2).

Traditionally all graduates of Haverford College go on to the University of Pennsylvania Medical School. Frank was on the waiting list when he was accepted at Syracuse. He chose Syracuse and, after the longest engagement of their class, married Frances Smiley Jones on May 30, 1942, and we are so pleased that Frank's wife is here with us today.

While at Syracuse Medical School, Frank took on numerous part-time jobs. Some of the nights were spent as an orderly at a local mental institution. He purchased an older home, renovated it, planted grass, and studied. While Frank built toys for the children, Frances ran a nursery school in the house, and extra rooms were rented to foreign students. Following graduation in 1950, Frank interned at Charity Hospital in New Orleans, having been inspired by a Westtown Preparatory teacher who left while Frank was there to work with sharecroppers in the South. The following year, he entered general practice in Chatom, Alabama, as the only physician in a 60-mile radius. Between 1951 and 1956, as the family grew to include three boys and three girls, later to be joined by another boy, he was caring for approximately 5,000 patients per year; he was his own laboratory technician, and all tasks of the practice were his. He referred all surgery to the nearest facility, some 50 miles away. For this reason, in 1956, he moved to Harlan, Kentucky, taking a position as general physician at the Miners Memorial Hospital. The following year (1957) he began his general surgery residency and with preposterous perspicacity and inspired audacity began working (alone) on a totally implantable artificial heart.

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WESTTOWN SCHOOL
WESTTOWN, PA.

OFFICE OF THE PRINCIPAL

4 27 1937

Mrs. Willard S. Hastings
45 East Church Road
Elkins Park, Pa.

Dear Friend:

We are a little aghast at the thought of Frank trying to qualify for Haverford, first, because his rating is such that the passing of College Boards is somewhat questionable, and second, because his units do not exactly fit Haverford's requirements. As thee probably remembers, he is offering two units in each of two languages rather than three and two, as Haverford requires. Ordinarily, they do not grant credit either in Civics or General Science. Perhaps thee talked over these matters with Dean MacIntosh, or perhaps by taking extra courses in college this deficiency can be made up. Our attitude in the matter will depend quite largely on the encouragement that Dean MacIntosh gives after examining his record.

Very sincerely,

James F. Walker

JFW:H

Principal

Figure 2--Letter from the principal of Westtown School to Frank Hastings' mother, April 27, 1937.

Somebody said that it couldn't be done,
But he with a chuckle replied
That maybe it couldn't, but he would be one
Who wouldn't say so till he'd tried.
So he buckled right in with a trace of a grin
on his face. If he worried he hid it.
He started to sing as he tackled the thing
That couldn't be done--and he did it!

Edgar A. Guest
"It Couldn't Be Done"
The Path to Home, 1919

More specifically, on July 14, 1958, Frank wrote a remarkable letter to The Holter Company, 3rd and Mill Streets, Bridgeport, Pennsylvania (figure 3).

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HARLAN MEMORIAL HOSPITAL

MINERS MEMORIAL HOSPITAL ASSOCIATION

Harlan, Kentucky

July 14, 1958

The Holter Company
Third and Mill Streets
Bridgeport, Pennsylvania

Dear Mr. Holter:

I am at present involved in a research project which will consist of implanting an artificial heart within the body. It has been my plan to make this device of silicone or at least cover it with silicone. Dr. R. R. McGregor at the Dow-Corning Corporation in Midlands, Michigan, has given me your name as someone who is equipped to handle silicone and knows a good deal about its idiosyncrasies. I would like to know a little bit more about your set-up and what you are prepared to do.

If I make a drawing of the device which I wish to have made will you make the mold as well as the final article from silicone? Do you also make things from stainless steel which would require considerable lathe work? It was my original plan that I would have to have the mold made one place, the silicone casting made at another place, and the mechanical portion of the device made at still a third place; it has been my understanding from talking with Dr. McGregor that you would probably be capable of doing the entire job yourself. Is this correct?

Very sincerely yours,

Frank W. Hastings, M.D.

FWH/abb

Figure 3--First letter from Frank Hastings to John Holter, July 14, 1958.

As was his nature, he simply stated "I am at present involved in a research project which will consist of implanting an artificial heart within the body . . . . It has been my plan to make this device of silicone, or at least cover it with silicone. If I make a drawing of the device . . . will you make the mold as well as the final article? Do you also make things from stainless steel which [would] require considerable lathe work?" Thus began a long and fruitful collaboration between Frank Hastings and John Holter. John Holter is here with us today, but I have been privileged to review their correspondence of that period. Hastings' letters to Holter dated July 28, 1958; September 5, 1958; September 15, 1958; September 30, 1958; October 20, 1958; October 24, 1958; November 18, 1958; December 3, 1958 ("I expect the heart alone to cost well in excess of $250"!); December 23, 1958; April 28, 1959; July 16, 1959; August 4, 1959; March 4, 1960; March 20, 1960; November 4, 1960; November 15, 1960; April 28, 1961; June 13, 1961; June 28, 1961; August, 1961, (Frank's NIH Grant Application for $7,000 to build an artificial heart was rejected . . . the United Mine Workers,

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however, granted $3,500); January 16, 1962; November 9, 1962; February 14, 1963 ("We will put the heart in the abdomen and run the conduits into the chest"); April 18, 1963; November 18, 1963 ("Why not a double-chambered heart powered by the respiratory action of the diaphragm and rib cage . . . of course one lung would have to be removed!"); January 20, 1964 ("Remove the right lower lobe, right middle lobe, left lower lobe and lingula! . . . then use McCabe's 'old' double ventricle enclosed in a partially rigid container containing a diaphragm in its right and left walls . . ."). The results of this collaboration (figures 4 and 5), now in the Smithsonian Institute, sustained an experimental animal for 32 hours.

On March 27, 1964, Frank wrote Ralph Knutti, M.D., then director of the National Heart Institute, confirming his conversation with John R. Beem, the then associate director, and evinced interest in coming to the National Institutes of Health. On July 6, 1964, Frank became Special Assistant to the Associate Director for Program Planning of NIH, and under his aegis, the Artificial Heart Program was born.*

Transition

Quite recently, I was fortunate to advise and collaborate with a rather large number of investigators in this and other countries in a reasonably comprehensive project involving articulations of the appreciation of

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*The previous year (1962-63), meeting repeatedly in Manhattan and Washington, the former Senator Lister Hill, Dr. Michael E. DeBakey, the late Dr. Sidney Farber, and Mrs. Mary Lasker wisely used both hindsight and foresight along with large measures of well-deserved biopolitical comprehensive project involving articulations of the appreciation of influence to suggest that an Artificial Heart Program be initiated under the aegis of the National Institutes of Health and supported by public funds. Within a year, Dr. Frank Hastings was recruited from Wise, Virginia, to head up a broad-based, multidisciplinary program drawing on established expertise and resources throughout the country, announced in the Federal Register along with requests for proposals. Six industrial/academic consortia were selected by national, competitive peer-review: Convair Division of General Dynamics in San Diego; Hamilton Standard of Windsor Locks, Connecticut; AVCO/Everett Research Laboratory in Massachusetts; Stanford Research Institute of Menlo Park, California; Westinghouse Electric Corporation of Pittsburgh and Harvard Thermoelectron in Boston. From the outset, the Program was conceived of and viewed as a partnership for progress with peer review, open to public scrutiny, between industry, academe, the individual investigator(s), and Federal auspices.

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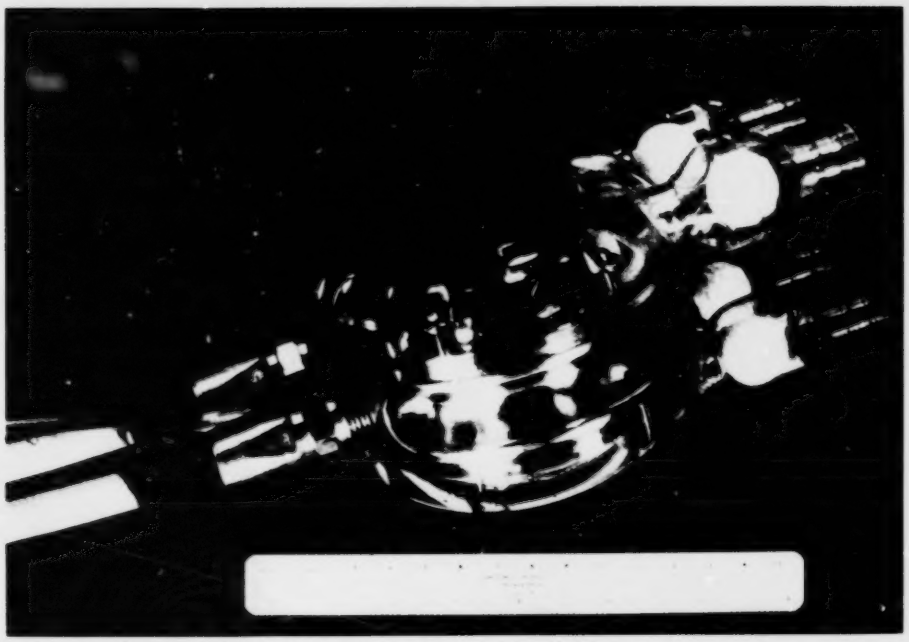

Figure 4--Hastings-Holter total artificial heart, circa 1960.

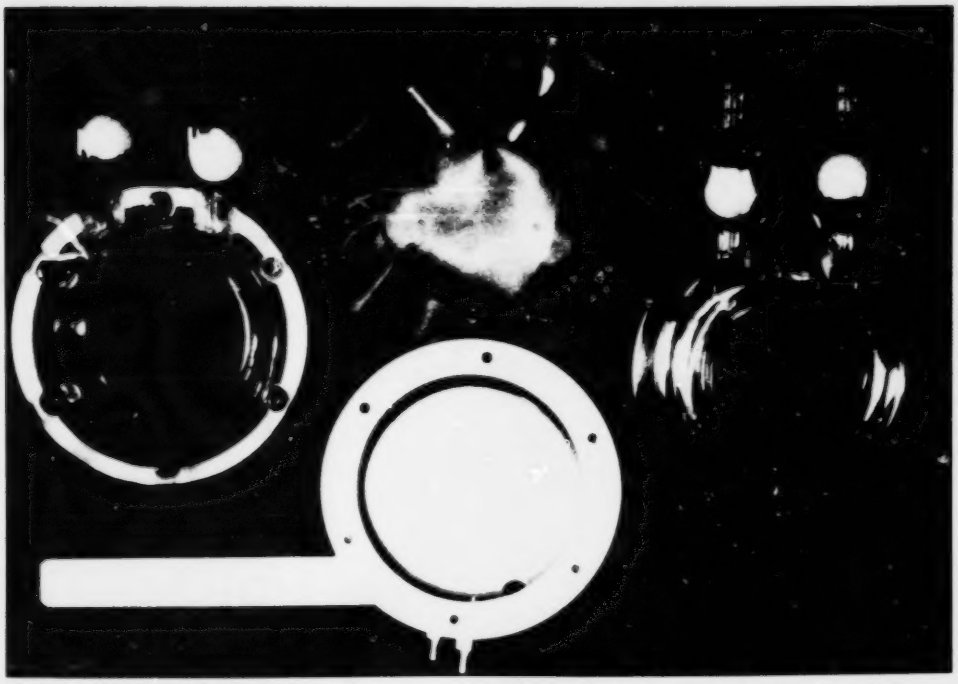

Figure 5--Components, Hastings-Holter total artificial heart, circa 1960.

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science.* An extensive number of ideas and areas were explored. After much discussion and considerable interplay, the 33 abstract approaches we initially isolated are:

analogy	creativity	observation
analysis	definition	order
antithesis	differentiation	parameters
association	elimination	perception
assumption	experimentation	play
categorization	fantasy	serendipity
causality	feedback	simplification
chance	hypothesis	substitution
classification	incubation	synthesis
confirmation	innovation	thesis
combination	metaphor	verification

These abstractions are the result of rather prolonged thought, debate, and dialogue among representative members of the international scientific and educational communities along with wide-ranging conversations regarding the history and philosophy of science, the origins of creativity, and the peregrinations of scientific endeavors. We, all of us, decided that all of our activities consisted of one, several, many, or all of these categories. It does not require much extrapolation to fit Frank Hastings and artificial heart development again into one, many, or all of these categories.

Speaking as Frank's surrogate, today, I am not sure which of these categories or approaches he would have valued most. I personally believe that I value creativity above all others because it is such a rare commodity. Be that as it may, let us continue our conversations by moving on to a further distillate of these techniques or procedures that are essential to all problem-solving processes, i.e., at higher magnification, our group proceeded from these 33 interrelated abstract approaches to nine essential problem-solving techniques. To close the loop, I would like to share my interpretation(s) with you in returning to our topic: The Hastings File: A Search for Solutions. I believe that we, all of us, employ each and every one of the following methods, as Frank did, at one time or another. A restatement of these first principles vis-a-vis the Artificial Heart Program is my major thrust. These nine following approaches are infinitely relevant and always applicable. An occasional return to these fundamental approaches in the cold grey dawn in our continuing attempts to see things clearly and to understand them completely seems particularly worthwhile. They could be termed the nine stepping stones across any gulf of incomprehension. They are:

1) investigation
2) patterns

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*The Search for Solutions, 708 Third Avenue, New York, New York 10017.

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3) trial and error
4) context
5) adaptation
6) modeling
7) prediction
8) evidence and
9) theory

Now let me share with you what I learned from Frank Hastings and the Artificial Heart Program, beginning in 1964.

Frank Hastings and Investigation

Investigation is the basic process of science, i.e., observation, acted upon by thought. In somewhat different settings, it is what Dame Agatha Christie and Sherlock Holmes (Sir Arthur Conan Doyle) did when collecting impressions or facts, subsequently organizing and/or synthesizing them into meaningful structures.

Frank Hastings knew full-well the supreme value of investigation and the individual investigator. He, himself, was an investigator. The enduring and recurrent approach of asking who, what, where, when, and most importantly why was his and our legacy. Frank knew, from experience in his laboratories in Harlan, Kentucky, and Wise, Virginia, from his long and variegated correspondence and collaboration with John Holter . . . that investigation was, and is, the sine qua non, that investigation was, and is, the first of the nine stepping stones across the great gulf of incomprehension. It may well be that at the outset, in 1957, he only directed his efforts at developing an artificial heart because at the time, it was incomprehensible, elusive, fleeting, and evanescent . . . an Everest, a Holy Grail. Can we teach the fascination of such an adventure . . . really high adventure? Can we transmit or impart to others this sense of excitement of hunting such elusive creatures of the mind? Frank wrote in 1957 that he would seek solutions in what was then a vast unknown. Nearly 30 years later, we look back with both nostalgia and admiration. For, over a 7-year peiod, he taught himself to be an investigator to such an extent that given the opportunity, he might inscribe his own epitaph thus: Frank Hastings, Investigator. Because of those initial efforts, today we have meaningful structures to refine, modify, and further advance, experimentally and clinically.

Frank Hastings and Patterns

Patterns underlie the structure of both the world and the mind. Because these patterns are related, we can understand the world and investigate it with confidence, secure in the knowledge that sooner or later, somehow it will all make sense. Patterns reduce problems to their essential order. Their symmetry and elegance help us to recognize the basic nature of things.

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When Frank Hastings first wrote John Holter in 1956 he may or may not have realized that he, along with Dale, Schuster, Demikhov, Salisbury, McCabe, Kusserow, Akutsu, and Kolff,* was initiating an odyssey of seeking patterns. By and with whatever means, not to mention with whatever talents, ingenuity, naivete, serendipity, perseverance, wisdom, or perhaps even stubbornness, he launched his worthy enterprise of constructing an artificial intracorporeal heart. He did not know that the launching of Sputnik that year would help trigger the era of Camelot in research and development, but he might have predicted that his search for solutions would result in patterns . . . patterns of success and failure, patterns of productivity and counterproductivity, patterns of promise, frustration, and ultimately, fulfillment. In retrospect, it is not difficult to imagine the enthusiasm, energy, and great expectations as Hastings set out. From the beginning, he might have anticipated that whatever he thought of, conceived, fabricated, tested in vitro and in vivo would establish inroads and set patterns for the future. Despite any lingering for simpler times and for easier choices, he was (and we are) committed to similar patterns of scientific thinking and technologic progress.

Frank Hastings and Trial and Error

Trial and error is the quintescence of learning, its archetypical mode--falling down and getting up--pioneering. Error is absolutely essential and quite creative. If a mouse in a maze gets it right the first time, it has not learned. Failure is positive information.

In articulating these thoughts for Frank, I know that he knew of their importance, having woven his way through this stepping stone in his

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* In 1928, H. H. Dale and E. H. J. Schuster in England devised what was probably the first diaphragm pump intended to replace the function of both the right and left sides of the natural heart. In 1937, Vladimir Petrovich Demikhov devised a compact apparatus consisting of two adjacent membrane pumps that performed the functions of both ventricles of the canine heart after their removal. Over the next 20 years, nothing substantive was developed until 1957, when Peter Salisbury of the Institute of Medical Research at the Cedars of Lebanon Hospital in Los Angeles "brought together several theoretical possibilities for prolonged supplementation of bodily functions by factitious means" and suggested that an artificial heart could be developed. At the same meetings, S. P. McCabe exhibited an implantable heart made of polyvinyl chloride and noted that such devices might be powered by external electromagnets rather than by fluid. The following year, Kusserow reported his initial experiments regarding "a permanent indwelling intracorporeal blood pump to substitute for cardiac function" (a right ventricular assist device) and Akutsu and Kolff reported initial experiments on "permanent substitutes for valves and hearts" (total artificial heart).

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laboratories in Harlan, Kentucky, and Wise, Virginia, before coming to NIH. As always, we are an impatient society, awaiting and expecting the latest "breakthrough" in science and technology with the 6 o'clock news (film at 11). The harsh realities of scientific investigation include acceptance and anticipation of wrong turns, wrong experimental designs, wrong assumptions, and wrong results. Otherwise stated, one of the luxuries of entering into the problem-solving process properly is the fact that there are no wrongs . . . only red flags indicating possible rights. All of us have been fortunate to have been blessed with an occasional "right" experiment and an occasional infrequent acquisition of a bit of new knowledge. We, all of us, have been able to sustain our laboratories with hard work, perseverance and productivity with trial and error . . . mostly error. Because trial and error were so fundamental and familiar to Frank Hastings, the process of studying the errors and all of the possible combinations and permutations of the elements constituting error gradually has been built into our collective thinking. The phrases "back to the drawing board," and/or "falling back and regrouping" are familiar to all of us. It is, nonetheless, important to note that without an inspired initial trial, there would be no opportunity for error; the implications are obvious.

Frank Hastings and Context

Context is described in Hans Christian Andersen's fable: The Ugly Duckling, i.e., a thing that means one thing in one setting means something altogether different in another. By imaginatively shifting problems into new settings or combining them with other problems, discoveries can be made.

We have always known that the gifted investigator sees more, much more of a problem than the chance or casual observer. To each problem, we bring our collective apperceptive masses of experience, whatever the disciplines involved. To view a problem within its framework as related to our frames of reference is to see it in context. To be able to distinguish its properties from those imposed upon it by its setting and those imposed by our perceptual habits and limitations is insight. The rare talent of extracting and asking the right question(s) from obfuscating context, of relentlessly dissecting and distilling these questions back to fundamentals and essence allows the expert investigator to examine the essentials, to view it or them from all angles, and to ponder the problem, pristine and unadorned in order to see it clearly in the hope of understanding it completely. How much detail is necessary or relevant? Which aspects, segments, or subsegments are relevant? Frank Hastings had this talent and imparted it to others. Once we have defined the problem and examined it, in and out of context, the solution, however remote, must be closer at hand. There remains today our need to increase the keenness of our observations, to cultivate the attitude that is constantly on the lookout for the unexpected, making a habit of examining every clue that knowledge and serendipity may present. Chance not only favors the prepared mind but also the prepared laboratory.

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Frank Hastings and Adaptation

Adaptation is a refined process that applies empathy to problem solving--it suits the answer to the question. In a sense, feedback is a systematic repetition of this process in situations where the problem and the solution are in continually changing relationships.

When Hastings first asked himself whether or not an intracorporeal artificial heart could (not should) be built, he probably answered yes. He even considered its emergency use in man, less than a year or two later . . . although it was far from ready. His adaptation, as a way of solving the problem, was to borrow the solution from the problem. In 1957, he may have borrowed from H. E. Flint's science fiction article published in Argosy in 1921.*

> It was of silver, shaped like a flattened egg and a trifle smaller than that laboring, human blood pump. To it was attached a pair of long, flexible silver pipes, which led to 'Billie' knew not where. And near one extremity, the egg was provided with eight curious nozzles . . . . The arrangement provided duplicate sources, in vest pocket size, of power for operating (this) mechanical heart. Electricity worked the air pumps, which in turn supplied the little silver egg--implanted in the patient--with both pressure and vacuum, while doubtless the artificial organ itself housed a valve system which did the rest. The regulating device kept the blood circulating at the proper rate. The surgeon seemed satisfied with it all . . . .*
>
> H. E. Flint
> "The Devolutionist" Argosy, July, 1921

Adaptation (borrowing the solution from the problem) is simple in the stating but a demanding and highly refined process in effecting. In considering what could be done with an artificial heart, Hastings used some of these potentials in solving the problems of fabrication.

Each and every remaining problem in artificial heart development and clinical application has had, and will have, many possible solutions. Some imperfect solutions in the past have created worse problems. Some current solutions are simply adequate; some are good, some are better, and some are excellent; but the best solutions suit the problem . . . they are both appropriate and "elegant." By this I mean, without fanfare

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* The similarities of this fantasy with current targeted research and development activities underwritten by the Devices and Technology Branch of NHLBI are remarkable. The 50- to 60-year lag-time between fiction and fact has been analyzed in other Federal reports, for example, Sherwin CW, and Isenson RS: First interim report on Project Hindsight. Washington, DC, Office of Director of Research and Engineering, June 30, 1966 (Revised October 13, 1966).

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or elaboration and utilizing readily available or developed concepts, materials, and technology with a minimum of effort or interruption, elegant solutions are perfectly adjusted to the size, scope, and system of the problem. An elegant solution is low profile and attracts little attention and is always to be sought. Simply put, Hastings set out in 1956 to build an intracorporeal heart from first principles. In so doing, he adapted anything and everything to his solutions. The approach has much to recommend.

Frank Hastings and Modeling

In an abstract sense, modeling is thinking out loud, a way to find truth without consequences. In a more tangible sense, models are simplified, idealized representations of real objects or situations; with their help, it is possible to test theories or predictions, in whole or in part. When a problem contains too many variables, modeling is often the only way to deal with it.

Frank Hastings knew and nurtured, among us, the value of modeling. More prosaically, we could ask in 1984 where we might be in artificial heart development without all of the electric analogues, the mathematical predictions and solutions, the breadboard prototypes and the agreement (or disagreement) of in vitro and in vivo predictive real-time and/or accelerated testing. Where might we be without all of the various animal models (murine, canine, porcine, bovine, ovine, and primate) we have utilized in this creative enterprise, since its inception. Such models reduce complexity, cost, and risk to manageable scales in our continuing search for least common denominators. The pulse duplicator(s) and mock circulatory loops distributed to contractors by the Program Office in the 1960's and early 1970's are other excellent examples of such models that are abstract or miniaturized descriptions of reality, simple representation of complex forms, processes, functions, phenomena, or ideas. Such models may be verbal, graphic, mathematical or functional. In many instances, to solve a problem, no intelligent decision is possible without such models. By bringing ideas to an assessible, testable scale, models facilitate understanding and enhance prediction. We can understand more completely an idea or object when we identify it as part of a system in terms of structure, function, cause/effect relations, or combinations of such variables.

Frank Hastings and Prediction

Prediction seeks to foresee and manipulate consequences, to "get a leg up or jump on" the future of a problem with an eye to controlling what will happen, to minimize undesirable results, and to maximize desirable ones. Prediction is especially useful in checking the implications of theories.

As we generalize from one experience to the next by building categories from our observations, we all participate in the activity of prediction. It was predictable that someone, sooner or later, would make initial

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inroads into artificial heart development; it was equally predictable that some of the problems would be under- or overestimated, and it is currently predictable that with the advancing wave of technologic developments, current problems will be resolved . . . all for the greater good. The last nearly three decades of progress from the pollination of ideas to established disciplines and subdisciplines within the field were predictable. Reduced to essentials, the heart is only a pump . . . as such, it should be replicable in the laboratory and ultimately implantable. In the inevitable transition from Tom Swift to Jacob Bronowski, we are increasingly committed to such scientific ways of thinking and predicting with all of the attendant implications. We are further committed to a technologic way of acting, and we cannot go back. My friend, Issac Asimov, and my student, Michael Crichton, who unabashedly borrowed generously from the core curriculum of Harvard Medical School in writing their science fictions of the sixties and seventies (Fantastic Voyage/The Terminal Man) fairly accurately predicted some of the realities of the eighties. Our civilization may change in character, but we cannot reverse our evolutionary clocks. The genie of artificial heart development and clinical application is out of the bottle . . . it cannot be imploded. It was predictable.

Frank Hastings and Evidence

Evidence is information that fits into a pattern and helps prove or disprove a theory. It must be recognized, sought out, collected, verified and interpreted. It is a delicate process . . . and a noble enterprise. Everything is evidence of something, but it is sometimes difficult to determine of what.

Frank Hastings knew then (1957) as he looked about that something was in the wind . . . that something was predictable . . . the evidence was there. The nearly 30 intervening years have only confirmed his hypotheses, his predictions, his modeling, based on evidence. Even as we speak today, both spectators and players, there is an unprecedented series of events in the history of mankind, i.e., the exponential and explosive growth of the pure and biosciences along with all of the technologies. The evidence is all about us. Sorting out, categorizing, systematizing, prioritizing, and utilizing this evidence are the nature of science. It pervades every detail of our daily lives, our projects, our predictions, our goals, our hopes, and our dreams. This evidence will affect and alter all aspects of the 21st century from today more radically than our time has been altered from prehistory.

Prediction based on evidence allows us to test our hypotheses before entering the laboratory, before turning on our electronic spread sheets, before writing the proposals, before committing the funds, and before exerting the efforts of confirmation. Hastings knew and predicted this, and he knew that before any problem can be solved or even intelligently approached, one needs information, i.e., evidence. The evidence is there . . . it has always been and always will be there. Recognizing its quantity, quality, and nature will determine our

interpretations. Only our astuteness limits the process of its interpretation. Find the evidence and the future is ours. As one gifted wag* could be paraphrased, "We have found the (scientific) enemy and they are us (the investigators)." Eureka!!

Frank Hastings and Theory

Theory is a mechanism of explaining things we do not understand . . . jumping or leapfrogging to conclusions and then looking around from where we have landed . . . to see the world from there. Theories have the extraordinary power to explain and to set in motion the other processes of problem solving, but they are, by nature, temporary. No theory explains anything completely or forever.

Frank Hastings must have known that any theory suggests new theories, new experiments, and new realms to explore, thus enabling us to view, more clearly, any event, object, or phenomenon. Theory is the yeast of invention, the ferment of discovery, the catalyst for conception, and the purveyor of things to come. Theory provides a framework for our projected facts (or fictions); it should remain fluid and in flux, ready to be revised, refined, modified . . . or abandoned when contradicted by incontrovertible new evidence. The needed iconoclast luxuriates in dismantling and disproving the theories of others. In turn, and in response, those blessed with innate creativity generate new and newer theories based on feedback, realizing that a theory is good only as long as it is useful. In our own experience in artificial heart development and other investigations, we have had the great opportunity and good fortune to consult with, or to be taught by, a number of Nobel or near-Nobel laureates . . . outstanding theoreticians, all. John F. Enders (1954), Thomas H. Weller (1954), Andre Cournand (1956), Dickinson Richards (1956), George Wald (1967), Christian B. Anfinsen (1972), George E. Palade (1974), Norbert Wiener and Edwin Teller--all, in one way or another, had utilized these nine stepping stones across gulfs of incomprehension . . . world-class thinkers. Our heritage in Artificial Heart Research and Development and Clinical Application is now richer for some of the courses set by Frank Hastings. What we wish to do with this marvelous legacy remains to be seen. The challenge and opportunity are here.

SUMMARY

In summing up our conversations regarding the Hastings File: A Search for Solutions, let me ask (and answer) a series of seven Socratic questions. If Frank were here in 1984-85, I would imagine that he might think in these seven terms and pose an equal number of questions of this nature, i.e.,

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*Pogo

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1)	Situation	Where are we?
2)	Information	What do we know?
3)	Management	What do we do next?
4)	Estimation	Are we close?
5)	Outcome	Where are we going?
6)	Argument	Are we right?
7)	Restatement	How do we see things?

Q_1) Where are we? (What is the current situation with Artificial Heart Research and Development and Clinical Application?)

A_1) At the risk of incurring criticism rightfully reserved for institutionalized megalomanical immodesty, let us indulge ourselves briefly to recount some of the achievements of the Program. In fact, in less than three short decades--micromonths or nanoyears in the overall scheme of things--Artificial Heart Research and Development and Clinical Application has virtually raced from concepts to clinical realities. When Hastings and Holter began their investigations on an implantable total artificial heart in 1957-58, no less an authority than Stanley Sarnoff, then at NIH, stated that year (correctly) that "it would be likely that space travel would be a reality, before these efforts were clinically successful." Currently (1984-85), these ideas are no longer far fetched, and families of pneumatic, electric, and thermally actuated systems have been evolved. Pneumatically driven implantable left ventricle assist devices have undergone Federal reviews and approval for first- and second-phase clinical trials. Thermal systems have been implanted in animals to demonstrate short-term feasibility, and long-term (greater than 2 years) electrically activated systems are currently entering phase III of development and experimental testing. Total artificial hearts have been implanted clinically, and the pace is quickening. The Hastings File is certainly far from closed. Rather, it is just unfolding.

Q_2) What do we know? (What is the extent, depth, and breadth of our relevant information?)

A_2) In 1984-85, we know now what John Kenneth Galbraith meant when he wrote in response to my inquiry two decades ago regarding whether or not an artificial heart could (or should) be developed. He answered prophetically "In order to make rabbit stew, first catch a hare. . . ." We now understand the wisdom and prescience of this meticulous metaphor and now find that Artificial Heart Research and Development and Clinical Application is a burgeoning discipline, a discipline that will not lie still for physical examination, with its own well-established sources, resources, literature, protocols, precedents, procedures, rationales, evolving and predictable outcomes, and new initiatives. Our current information is increasing exponentially and will continue to do so with each refinement, modification, or giant leap forward. Quite simply, the Hastings File is getting larger.

Q_3) What do we do next? (What is the optimal use or management of our efforts and resources?)

A_3) It would seem that one of our next orders of business could be found in a careful review of the NHLI Implantable Circulatory Support System Development strategy spanning the years 1967-85 (figure 6). When Hastings and Harmison and Huffman and the various contractors developed this scheme, they could not predict what the future actually would bring. The passage of time has shown with remarkable parallels the relative accuracy of these inspired predictions. Nonetheless, there is much left to be sought, learned, and realized in this graphic projection of the Hastings File and our search for solutions.

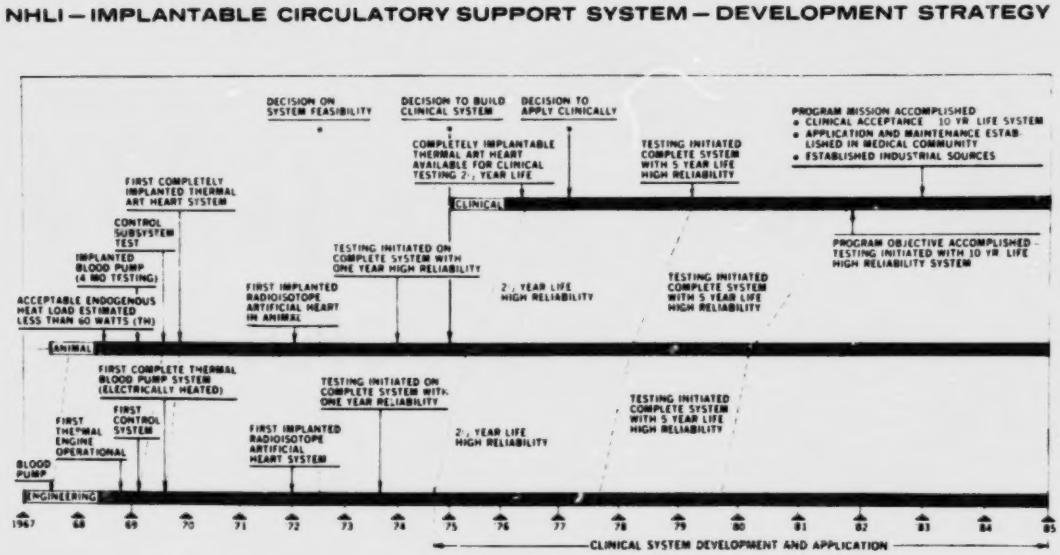
NHLI—IMPLANTABLE CIRCULATORY SUPPORT SYSTEM—DEVELOPMENT STRATEGY
DECISION ON SYSTEM FEASIBILITY
DECISION TO BUILD CLINICAL SYSTEM
DECISION TO APPLY CLINICALLY
PROGRAM MISSION ACCOMPLISHED
• CLINICAL ACCEPTANCE 10 YR LIFE SYSTEM
• APPLICATION AND MAINTENANCE ESTABLISHED IN MEDICAL COMMUNITY
• ESTABLISHED INDUSTRIAL SOURCES
COMPLETELY IMPLANTABLE THERMAL ART HEART AVAILABLE FOR CLINICAL TESTING 2½ YEAR LIFE
TESTING INITIATED COMPLETE SYSTEM WITH 5 YEAR LIFE HIGH RELIABILITY
FIRST COMPLETELY IMPLANTED THERMAL ART HEART SYSTEM
CLINICAL
CONTROL SUBSYSTEM TEST
IMPLANTED BLOOD PUMP (4 MO TESTING)
TESTING INITIATED ON COMPLETE SYSTEM WITH ONE YEAR HIGH RELIABILITY
PROGRAM OBJECTIVE ACCOMPLISHED TESTING INITIATED WITH 10 YR LIFE HIGH RELIABILITY SYSTEM
ACCEPTABLE ENDOGENOUS HEAT LOAD ESTIMATED LESS THAN 60 WATTS (TH)
FIRST IMPLANTED RADIOISOTOPE ARTIFICIAL HEART IN ANIMAL
2½ YEAR LIFE HIGH RELIABILITY
TESTING INITIATED COMPLETE SYSTEM WITH 5 YEAR LIFE HIGH RELIABILITY
ANIMAL
FIRST COMPLETE THERMAL BLOOD PUMP SYSTEM (ELECTRICALLY HEATED)
TESTING INITIATED ON COMPLETE SYSTEM WITH ONE YEAR RELIABILITY
FIRST THERMAL ENGINE OPERATIONAL
FIRST CONTROL SYSTEM
FIRST IMPLANTED RADIOISOTOPE ARTIFICIAL HEART SYSTEM
2½ YEAR LIFE HIGH RELIABILITY
TESTING INITIATED COMPLETE SYSTEM WITH 5 YEAR LIFE HIGH RELIABILITY
BLOOD PUMP
ENGINEERING
1967 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85
CLINICAL SYSTEM DEVELOPMENT AND APPLICATION

Figure 6--NHLI, implantable circulatory support system--development strategy, 1967-1985.

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Q_4) Are we close? (What are the best estimates of our progress?)

A_4) An appropriate answer to the question, "Are we close?" is both yes and no. Or more vaguely "Some people would say yes . . . and some people would say no." And I tend to agree with them! On the one hand, major questions and problems have been answered and solved, most assuredly. On the other, there are major problems that cry out for further solutions. For example, is blood pump diaphragm calcification species-related, materials-related, flex-related, lipid-phospholipid-phosphoserine/release-related, or otherwise? Is this process as complex as native atherosclerosis or an accelerated form of its biologic analogue in the process of aging within a prosthetic device? Will the solution to this aspect of device progeria have major implications in the ultimate understanding of native atherosclerosis at large? With this aspect of the Hastings File, perhaps we are not close . . . but the problem has been defined.

Q_5) Where are we going? (What is the outcome of all of this?)

A_5) The answer to the fifth question should be self-evident. We are proceeding toward a totally implantable intracorporeal artificial heart, a totally implantable intracorporeal LVAD, a totally implantable intracorporeal RVAD, and all of the less ambitious variations and permutations along these central themes. These original objectives remain worthy, desirable and useful . . . but difficult and formidable in the obtaining. Make no mistake, in returning to first principles, these are, and will remain, the objectives. Only with their obtaining and widespread clinical use could the Hastings File possibly be closed.

Q_6) Are we right? (As always there will be arguments against, and critics of, these efforts.)

A_6) There will be continuing arguments as to whether or not we are right. Some will persuasively submit that we are wrong. We are not to worry; we are to take heart, so to speak, and to borrow from strong . . . yes, even Quaker convictions (Frank might like that) that the course he set was (and is) the proper direction.

Q_7) How do we (Frank and I, if you will) see things?

A_{7a}) As I see it, the broad spectrum of Artificial Heart Research and Development and Clinical Application is only yet another rather complex problem or series of problems in search of a solution(s).

A_{7b}) As I see it, the solution is further enlightened use of our now familiar nine stepping stones across the remaining gulfs of incomprehension (investigation, evidence, trial and error, patterns, context, modeling, prediction, adaptation, and theory).

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A_{7c}) As I see it, it is impossible to predict which new ideas, new insights, and new approaches will be useful, but the notion that they are, or will be there, is profoundly persuasive.

A_{7d}) As I see it, we must accept the inevitability of uncertainty in knowing that the most elegant, original, and relevant scientific work at any one time may require that the needed or desired methods be developed in parallel with the ideas and observations.

A_{7e}) As I see it, we must continue to perpetuate the preposterous, and, in so doing, we will be lifted successively and successfully into new trajectories of insight, understanding, and application in our worthy arena.

A_{7f}) And finally, of this I am certain. The Hastings File will remain open; it cannot be closed, and we cannot turn back. We will go forward and the future is bright . . . even incandesent. This is what I have learned.

Think of us kindly, as we will of you. You have our every good wish, and thank you, very much.

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Chairmen's Summaries

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Chairmen's Summary: Biomaterials Session

Dr. Sumner Barenberg
Dr. John Sharefkin

I. CALCIFICATION

The six presentations attempted to address the fundamental mechanisms, the transient formation of various calcium phosphates to hydroxyapatite, and new approaches to inhibiting calcification without understanding the primary mechanisms leading to calcification. It is recognized that there are initial foci of calcification arising from cell debris, thrombosis, and ion sequestering.

To understand the question of calcification, one must undertake a multilevel interdisciplinary approach, starting with a fundamental core, separating the various factors, and then integrating them. The historic and current work of Drs. Levy and Schoen outlines this approach with respect to bioprosthetic materials, and the works of Drs. Harasaki, Coleman, Lian, Singh, and others have addressed the calcification of biomaterials. Specifically, Dr. Levy's findings of the effect of residual aldehyde functionality and the interfacial interactions of ethanehydroxydiphosphonate (EHDP) (and/or diphosphonate (DP)) on calcification and calcification inhibition, respectively, here provided the needed foundation to begin to define the primary mechanisms of calcification. Further, Dr. Levy's detailed morphological studies of specific collagen calcification have provided a model into which the observations of Drs. Buchanan and Clarke Anderson can be incorporated. Dr. Buchanan has observed that the pretreatment of the pericardium with phosphate buffer leads to mineralization; whereas, pretreatment with acetate buffer does not (within the time frame studied). At this juncture, Dr. Anderson's model and Dr. Dewanjee's and others' observations need to be brought to bear. Collagen is not the material that blood, tissue, and/or the other ionic biological components interact with directly. Collagen is a core protein that is surrounded by a sheath of hydrophilic glycosaminoglycan (GAG) proteins. It is the GAG proteins that are at the interface unless the collagen has been deformed and/or denatured (see collagen deformation literature), at which point collagen will be directly exposed to the biological milieu. The GAG sheath is capable of sequestering ions that, with time and osmotic pressure, will diffuse through the hydrophilic sheath and selectively bind in regions of the collagen fibrils. This is where work like Dr. Brown's should be focused to obtain a fundamental understanding of the reasons for selective ion partitioning, crystallization, and subsequent crystal transformations. It will be this type of research that will afford us an understanding of the mechanisms of bioprosthetic calcification.

Dr. Singh is approaching calcification from a developmental point of view. He notes what may be a meta stable calcium phosphate plaque forming on smooth surfaces. These plaque-type crystals may be the

precursor deposits that will either eventually transform to hydroxyapatite or embolize. He does not, however, have any hard evidence as to whether these plaques are calcium phosphate or transient artifacts. Dr. Singh needs to define his control surfaces with respect to specific surface chemistry and the presence of any microvoids or crazes that could serve as a nidus for deposition.

Dr. Lian has drawn attention to physiologic control of calcific deposit degradation due to the presence of osteocalcin, by virtue of its chemoattractive properties to recruit resorbing cells to the sites of the deposit. Osteocalcin as well as alkaline phosphatase are indicative of rapid growth and may be interrelated to calcification. The question that we come back to in Dr. Lian's work and that of Drs. Singh, Dewanjee, Levy, Buchanan, and Brown is the relevance of calcification in the animal model relative to the clinical situation.

Dr. Dewanjee is approaching calcification from another standpoint. Dr. Dewanjee recognized the effects of residual aldehyde functionality on calcification, as did Dr. Levy, and has begun to immobolize DP and similar analogues onto his surfaces to inhibit calcification. Based on his experimental evidence and the works of other groups, I anticipate that this approach will be usable.

In summary, this brings us back to the key issues: (1) the etiology of calcification and (2) the physiological differences and significance between the evaluated animal model and the clinical situation. It appears from the presentations today that the initial calcification events differ between bioprosthetic and synthetic prosthetic surfaces but, with time and after the formation of $Ca_8H_2(PO_4).5H_2O$ (OCP), proceed along a common pathway. It is apparent from today's presentations that the need for using well-defined and characterized surfaces as well as the need for developing a standard set of calcification reference materials, for example, telopeptide-cleaved renatured collagen, should be addressed.

Dr. Galletti's presentation, using Vicryl woven bioresorbable vascular grafts, poses more questions to the complex issues of the necessary factors needed in designing cardiovascular grafts. The questions of compliance versus noncompliance, porosity versus smooth, hydrophilic versus hydrophobic, immobilization, prophylactic anticoagulants, and antiplatelet drugs are of current concern. The issues that Dr. Galletti's work will pose are: (1) What are the effects of having a bipolar cell, such as endothelium, associated with a dynamic scaffold during the time course? (2) Having a collagen matrix develop as the Vicryl is resorbed may lead to enhanced calcification, as noted in the bioprosthetic area. (3) Will a resorbing scaffold afford smooth muscle infiltration? These issues and those already being addressed will add a new and exciting dimension to the cardiovascular research area, with the concepts of tomorrow being addressed today.

Dr. Ratner presented the cytotoxic effects of hydrophobic and hydrophilic polymers on 3T3 cells. This test may be sensitive to low-

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molecular-weight contaminants associated with polymers or cytotoxicity. However, the clinical relevancy of this approach will need time and an expanded data base to tell whether it will be relevant.

II. SMALL VESSEL PROSTHESES

Seeding of polytetrafluoroethylene (PTFE) and Dacron small diameter vascular prostheses with autogenous endothelial cells grown in culture, originally done in dogs, has been extended to baboons, using only small segments of cephalic vein as cell sources for culture. Although spontaneous endothelial coverage of grafts in baboons may blunt observed differences between seeded and unseeded grafts, significant decreases in Indium-111-labeled platelet accumulation were seen on seeded grafts in parallel with greater endothelial coverage. These findings and the development of noninvasive study of grafts by external gamma imaging lend support to hopes for clinical adoption of endothelial seeding and its quantitative study in patients.

Human umbilical vein endothelial cells have been used to compare polyester elastomer prostheses with and without gelatin, fresh fibrin, and fibronectin coatings as substrates for in vitro endothelial cell growth on prostheses, with no major differences found in cell division rates or resultant surface coverage; large losses (50 percent) of these cultured cells from prostheses, either during or shortly after implantation, have been measured by isotope labeling methods and suggest that early endothelial losses from mechanical or shear stresses during or after implantation are a problem that needs to be addressed in using prostheses "prelined" in culture. Encouraging histologic evidence has been obtained of at least partial endothelial coverage of one PTFE graft in a human patient following autogenous endothelial seeding.

Comparison of compliant and noncompliant grafts with similar flow surfaces strongly suggests that improved patency might be gained from compliance matching; but, even with these grafts, large variations in compliance still occur over short distances near suture lines and are being examined as a possible cause of perianastomotic intimal hyperplasia. Two- to threefold variations in compliance in a 3 to 5 mm-wide zone may contribute to excessive cyclic stretching of host vessel smooth muscle and combine with vessel injury and platelet deposition to produce hyperplasia from several mechanical and nonmechanical causes. Both interrupted and continuous anastomoses and compliant and noncompliant grafts appear to be liable to perianastomotic hypercompliance.

Studies of absorbable graft materials in rabbit aortic prostheses have been done with both polyglycolic acid (PGA) and Dacron; PGA inner and outer capsules appear to be much thicker, and PGA produces less foreign body reaction and more complete transmural cellular growth than Dacron. PGA also appeared to facilitate growth of neointima, but it must be remembered that most grafts of this length will eventually acquire

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endothelial linings in most mammalian species. Ingrowth into PGA appears to involve slow alteration of invasive fibroblasts into cells more nearly like smooth muscle cells closer to the flow surface. Higher rates of phagocytosis of absorbable materials appear to promote more rapid healing without altering the final histologic results. Mechanical strength appears excellent after healing of such short segments, but whether it would be retained in segments with much longer length-to-radius ratios is uncertain. Even so, the rabbit PGA model may give important information about deleterious effects of present Dacron prostheses on cellular ingrowth.

Canine trials of carotid artery grafts using homologous carotid artery made acellular by detergent extraction, which preserves subendothelial basement membrane components such as type IV collagen and laminin, have been done with 2.5 mm diameter, 9 to 12 cm long grafts compared with similar grafts with the basement membrane altered by cross-linking with glutaraldehyde. Preservation of basement membrane gave higher (75 percent) 150-day patency rates correlated with sustained endothelial pannus ingrowth leading to complete endothelial coverage. In contrast, grafts with basement membranes altered by cross-linking had low endothelial pannus ingrowth that stopped after 1 to 2 cm. Although homologous human arteries may not ever serve for detergent extraction and clinical use, these results shed important light on the mechanism of stoppage of pannus ingrowth due to inappropriate alterations in the growth surface confronting the endothelial cells. Hence, they may be very relevant to extracting maximal growth from small numbers of seeded cells by deliberate design of graft surface chemistry.

An arteriovenous shunt model using easily removed Dacron segments (4 mm ID) inserted into the shunt was used to study deposition of Indium-III-oxine-labeled platelets in baboons. Labeling did not appear to discriminate among platelet populations of different sizes. Furthermore, insertion of grafts on successive days showed high reproducibility of the time pattern of deposition of successive days. Placement of grafts was well correlated with circulating beta-thromboglobulin levels; platelet count was seen to markedly affect deposition and should probably be recorded in similar studies comparing platelet deposition. Distribution of platelet size, density, and adenosine diphosphate (ADP) content were not affected by radio labeling. Large, dense, and granule-rich contents appear to be selectively removed at Dacron graft surfaces. Goretex graft material appeared to have far less platelet deposition than Dacron. Increasing fibril length of Goretex over the range 30 to 60 microns raised platelet deposition substantially.

Aspirin and dipyridamole in combinations remained the drug regimen with the sharpest accompanying drop in platelet deposition. This model appears to offer major advantages for studies of endothelial seeded prostheses in the first days after implantation because it allows data to be generated without sacrifice of large numbers of baboons. It should, therefore, be useful for studies of how to improve endothelial

cell adherence to graft materials without an excessive amount of early platelet deposition.

SUMMARY

It is fair to say that many of these studies are converging on the issue of deliberate design of graft surfaces of both texture and matrix-molecule composition to facilitate endothelial cell growth and attachment that can be sustained long enough to resist fluid shear and let endothelium grow to confluent coverage. A central problem is to combine these properties with a low enough level of material-platelet interaction to prevent thrombosis before endothelial coverage occurs. If this can be done, noninvasive external platelet imaging and plasma beta-thromboglobulin levels may provide an acceptable way to confirm whether endothelial coverage has been achieved.

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Chairmen's Summary: Energy Transmission Systems and Mechanical Circulatory Support Sessions

Dr. Edwin Alderman
Dr. Lee Baker
Dr. Hynda Kleinman

I.

Two transcutaneous systems, in pigs and dogs, were discussed. These tests had been of relatively short duration (maximum 30 months), but infection was not a major problem as is seen with the transcutaneous systems. Fibrocellular capsules did form around the implants as expected in response to a foreign body. In both cases, the skin between the implant and the external primary transformer appeared normal, and hair grew back in a normal manner. The size, shape, and ease of implanting and postimplantation care appear good for the transcutaneous devices.

Two groups presented reports on percutaneous systems used in pigs. The percutaneous devices in the past have had problems with recurrent infection due to incomplete contact between the skin and the device. One contractor claimed all the failures at 1 to 2 years were due to infection. Another group has attempted to improve the contact of skin to the implant and thus reduce infection by precoating the region passing through the skin with fibroblasts from the patients. It appears that epithelial down growth was retarded, and good contacts were made. No antibiotics were used. Whether the fibroblasts contributed directly to the formation of good contacts or the matrix deposited by these cells was the active agent is not known but should be pursued. It is clear that using fibroblasts has the disadvantage of requiring these cells to be grown out from the patient well in advance (2 months) of the procedure. Once the factors are defined for the fibroblast study, this time problem should be resolved. Because this is a critical problem that affects other potential systems, efforts should be made to find compatible surfaces for fibroblasts that stimulate rapid fibroblast repair reactions. An alternative and useful approach might be to find factors that retard epithelial cell growth down into the wound sites.

II.

Dr. Kurt Dasse reported the work at Thermedics, Inc., in association with the New England Medical Center in developing a transcutaneous energy transmission (TET) system in the form of a small compact transcutaneous transformer. The geometry of the system is such that proper alignment of the implanted and external coils is very simple and easy to maintain. Using miniature pigs, studies were undertaken to evaluate the biocompatibility of the materials, study the tissue response to the thermal and radio frequency characteristics of these systems, determine

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whether the size and shape of these devices were suitable, study the ability of the skin overlying the implanted coil to regenerate if traumatized, and determine the extent to which system migration occurred. The results of all these tests were very encouraging, with no adverse responses after 22-1/2 months of testing. There was no difference in the tissue response between unpowered and powered TET systems. The implanted secondary coil was walled off with a dense collagenous capsule only moderately vascularized, and the surrounding tissue remained well vascularized and normal in structure, tone, and vitality. The implant site was well perfused and regenerated when injured. The skin under the primary coil appeared entirely normal. No evidence of migration was detected. From these observations, the Series II TET system appears to be well accommodated by the host and is satisfactory for long-term transmission of energy.

Mr. David LaForge described the Novacor belt skin transformer (BST), which consists of a pair of narrow, flexible, concentric coils placed around the waist--one internal, the other external. Long-term in vivo evaluation was conducted in 8 days. Six of the eight implanted secondaries remained in place for at least 1 year. Infection prompted the termination of one experiment, and a second animal was lost to unrelated causes. With the exception of these two animals, the tests averaged more than 20 months, with the longest exceeding 29 months. There were no adverse effects from the chronic magnetic fields. The delivered power across the BST was 15 watts. The input power was 18-1/2 watts. Explanted belts were in excellent condition and enclosed in a thin, compliant, tissue capsule. The results of this study indicate that the BST is a suitable means for transferring electrical energy across intact skin for supplying long-term circulatory assist devices.

Turning from transformer systems to transmit electrical energy across intact skin, Mr. Paul Freed reported on the development of a percutaneous access device (PAD) that allows the passage of electrical or hydraulic lines through the skin. The project has investigated a technique to establish a biological seal between the PAD and the surrounding tissue by autologous fibroblasts grown on the transcutaneous portion of the PAD neck. It was observed that, in vitro, the fibroblasts form confluent multilayers and extend cell processes into the nanopores in the PAD neck. Upon treating the PAD with fibroblast cooling, epithelial migration was usually inhibited. In vivo testing appeared to bear out that in the majority of cases, the current implants are clinically satisfactory and that in histological evaluation of those that have failed, the inhibition of epithelial downgrowth was clearly demonstrated.

III.

Reports on left ventricular assist systems (LVAS) suitable for long-term human use were provided by seven groups of investigators. Thermal devices were discussed by two investigators.

Two electrically powered devices using differing motor and cam arrangements to power pusher-plate pumps were presented. Mr. Steve Igo showed an integrated system comprising a pusher-plate pump and electrical mechanical energy converter as a single unit (190 cc, 400 gms), an implantable control power module with 30-minute battery, a volume compliance chamber (230 cc, 80 gms) and external power supply/monitoring unit. In vitro testing has achieved maximum pump and energy converter lives of 6.6 and 3.4 years, respectively. In vivo studies over the past 2 years have achieved specifications of 90 ml/beat stroke volume with 10 l output. Four calves have survived implants to a maximum of 6 months. In an exercise study, the resting cardiac output of 6.6 l/min increased to 9.9 l/min, with a heart rate increase from 73 beats/min to 110 beats/min at constant stroke volume of 90 ml. Controller circuitry provided the option of ECG synchronous counter pulsation (mean cardiac output 7.1 l/min) or computer triggering based on adequacy of filling (mean cardiac output 8.7 l/min). Marked formation of inflow pannus has been managed by anchoring the biologic lining to the graft wall and by substantial conduit shortening.

Mr. David Gernes described an integrated LVAS developed by Thermedics, Inc. and Children's Hospital Medical Center. An integrated low-speed DC brushless motor via two rotating cams powers a pusher-plate pump at 1 cycle/rev. Its features include high efficiency, small number of moving parts, and unrestrained diastolic filling (405 cc, 870 gms). The implanted controller and 40-minute battery (160 cc, 360 gms) and variable volume chamber (230 cc, 80 gms) complete the integrated system. An interesting feature is the molding of an elastomer in the variable volume chamber to provide a restorative force to assist the LVAS filling. Power requirements were 7 watts at 8 l/min output at 120 torr. The pump/energy converter and controller are contoured for abdominal placement and the compliance chamber for pleural location. Five calf studies of the MK IV LVAS have achieved a total of 174 experiment days with a maximum study duration of 77 days. Mr. Gernes commented on the potential of rechargeable lithium batteries, which could reduce weight and volume of the external battery pack by 33 percent to 40 percent, although at a possible sixfold increase in cost.

Dr. Robert Kung, representing a consortium of Massachusetts General Hospital (MGH), Draper, NuTech, and University of Utah, described a system of two serial chambers, each with a hydraulically powered diaphragm. Fluid alternately delivered to each chamber by a single electrohydraulic pump powers blood flow and provides for builtin compliance chambers. Based upon prior MGH experience with nonporous surfaces, the LVAS uses a molded shape with integrated trileaflet valves at inlet, outlet, and between the two chambers.

Mr. Ken Butler described the Nimbus/Cleveland Clinic Foundation electrohydraulic LVAS. The energy converter location on the back of the pusher-plate pump and its subcutaneous thoracic location (rib removed) provides simplified access for repairs. This module (760 cc, 1,300 gms)

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along with an abdominal-implanted 30-minute battery (180 cc, 250 gms) and subclavicular Thermedics transcutaneous energy transmission system completes the package. Calf testing has achieved a maximum duration of 91 days. Interesting features include a system to transmit diagnostic signals across skin using an implanted dipole source. The use of two animals sharing different implanted modules seems a useful method to facilitate in vivo testing so that failure of a nonpump component does not lead to loss of the experimental calf outfitted with the energy converter/pump.

Dr. Peer Portner described the present status of the dual pusher-plate sac-type pump developed by Novacor and Stanford Medical Center. The balanced solenoid design minimizes undesirable motion. Synchronous operation at rates to 180 beats/min, 11 liters output and aortic mean pressure to 160 torr has been demonstrated. An implanted abdominal subcutaneous controller with 30-minute battery (150 cc, 360 gms), a belt-type transcutaneous energy transfer package, and compliance chamber complete the system. In vitro endurance testing has achieved a maximum of 5.7 years. In vivo testing in calves, particularly those over 100 days, revealed substantial inflow obstruction and calcification. Dr. Portner was encouraged by more recent tests in sheep, suggesting that pannus formation and calcification may not be so significant a problem as with calves.

In general, the presentations were useful in providing perspective on the development, evolution, and refinement of existing systems. Miniaturization and sophistication in materials, engineering, and system integration are evident. As investigators move into in vivo testing, it is apparent that a new phase of "trial and error," as eloquently described by Dr. John Norman in his Hastings Lecture, will become of paramount importance.

Failures of all types were touched on by various workers on mechanical assist devices. However, presentation in the future of the specific modes of failure, with investigator responses, changes, and tinkering, is always helpful to other people working in this field. Although informal conversations, coffee breaks, and exhibits provide important opportunity for individual interchange, presentations of real experiences in a group setting may be more helpful than general restatement of technical performance goals to others.

In vitro testing to date fails to approach the stresses of ordinary human existence. It would seem unfortunate to abruptly expose devices to long-term in vivo testing without the opportunity to learn from failures that will occur in strenuously demanding in vivo settings. Features of the human biological environment include not only temperature, corrosive tissue fluid environment, blood viscosity and filling characteristics but also include considerations of changing posture, acoustic energy, and rapid transients in filling and impedance characteristics associated with coughing, defecation, and bending. Fibrin

and pannus deposition on the biomer pump sac might, over extended periods of time, affect its compliance.

Animal testing has not fully considered the clinical circumstances common in patients in whom these devices will be used. The dysfunctional left ventricle commonly has mural thrombi with potential for embolization. Similarly, such patients are prone to rhythm disturbances, including rapid tachycardias of abrupt onset, with which the sensing controller circuitry would have to cope. Hemolysis, altered platelet lifespan, and conduit kinking with changes in body habitus and position may present future problems. It is, however, clear that the investigators of LVAS devices, in conjunction with the Devices and Technology Branch, are planning a highly structured, coherent, and rigorous testing program. As the testing becomes more rigorous, it is reasonable to anticipate that further device modifications will be required and are desirable, if one is to achieve the ultimate goal of an implanted assist device.

It is also important for developers of LVAS devices to rapidly integrate the feedback that cardiovascular surgeons will provide as they test initial devices in man. It is important to keep in mind the major applications for an LVAS: (1) the patient with end-stage congestive heart failure, (2) the postcardiotomy patient with shock, (3) the postinfarction patient with shock, and (4) a bridge to cardiac transplantation. For each clinical application, there may be a significant difference in the manner in which implantation is carried out, including conduit connections, location of implanted modules, and controller circuit parameters.

IV.

Dr. Portner reported the development of an implantable, permanent, ventricular assist system (VAS) suitable for long-term human use. This is an integrated system incorporating the balanced MK22D solenoid energy converter coupled to a Model IVA dual pusher-plate sac-type blood pump. As part of the system, an implantable microprocessor-based electronic control and power subsystem has been designed that responds to a wide range of physiologic conditions to control solenoid closure through a unique feedback servo system. Power and communications are provided by the belt skin transformer with backup power available from internal, rechargeable NiCd batteries. During the past year, in vivo experiments were continued with the MK22D/IVA system. A successful transition was made from the bovine to the ovine to provide a more suitable animal model. In the ovine, in an ongoing experiment, a pump output of 10 l/min has been sustained with no evidence of inflow conduit occlusion after 5 months of continuous synchronous operation.

Mr. Butler reported on development of the Nimbus-Cleveland Clinic Foundation E3C left heart assist system for patients requiring chronic cardiovascular support. This system is unique in that it is designed for total implantation within the thorax, and the surfaces in contact

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with blood have a biolized gelatin coating. This past year was the last in the 4-year development program of the E3C system. During this past year, major achievements were made in energy transmission, variable volume management, and diagnostic monitoring. An NHLBI transcutaneous energy transmission (TET) system was adapted to drive the E3C energy converter, and in vitro tests were conducted that demonstrated functional compatibility and satisfactory power range. Hermetically sealed NiCd cells in titanium housing were shown to provide satisfactory performance. Prototype wiring harnesses with titanium connectors are being tested in 37° C saline, and no trace of intrusion of water or ions has been detected after 3 months. A diagnostic monitoring system using signal transmission across the skin by a dipole source was developed to provide diagnostic signals that can be picked up by surface electrodes on the skin. Also during the past year, a hybrid version of the main E3C power supply and controller circuit was developed, and fabrication is nearly completed. An early E-2 system has now surpassed 4.7 years of operation without failure, and a newer E3C-1 system has been placed on endurance testing. The work of the past 4 years cumulated in the E3C-2 system, which, in a new program, will undergo extensive in vitro and in vivo testing.

Mr. Gernes of Thermedics, Inc. working with Dr. Bernhard of Children's Hospital Medical Center reported their progress in the development of the Mark IV system, which is a complete electrically driven ventricular assist system (VAS) intended for chronic cardiovascular assist together with a peripheral support and energy storage means that will permit a quasi-normal lifestyle. The Mark IV system consists of two implantable modules that can be powered from an externally worn energy source, either through a percutaneous lead or across intact skin. During the past year, in vitro testing of the Mark IV VAS has continued without incident or interruption for over 28×10^6 cycles. Tests of the elastomer diaphragm have exceeded 9.5 cumulative years without failure. The longest run has achieved 111×10^6 cycles. Also during the past year, five studies of the complete Mark IV VAS were conducted in calves, for a total of 174 experiment days. The longest study reached 77 days. The final 29-day study was powered by the TET system. Counterpulsation phasing was repeatable and responsive over the range of heart rate from 60 to 130 min. Flows up to 7 l/min were obtained. Mr. Gernes believes that the Mark IV VAS has met most, if not all, of the developmental goals contained in the NHLBI guidelines. Long-term in vivo evaluation of the system is in progress.

Mr. Igo and his coworkers reported progress toward development of a permanent, implantable, electrically powered ventricular assist system for use in patients with end-stage cardiac failure. All components of the system have been finalized, and a complete VAS has been fabricated and tested. Long continuous operation has been demonstrated. During the past year, in vivo studies have included two evaluations (over periods of 180 and 116 days) of a redesigned inflow conduit that eliminated occlusive pannus formation. In both evaluations, maximum blood pump stroke volumes of 90 ml/beat were obtained at a rest rate of 90 beats/min. At exercise, pump rates up to 120 beats/min provided an output

of 10.64 l/min. To date, 29 chronic studies have been conducted in calves with duration up to 6 months, providing cumulative in vivo experience of 5 animal years of testing. These results indicate that the system is capable of providing mechanical circulatory support for over 2 years and that it is now ready for preclinical validation.

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Chairmen's Summary: Diagnostic Instrumentation Session

Dr. James Bailey
Dr. Robert Kruger
Dr. John Reid

I.

Twelve investigators presented recent work funded by the NIH in two programs: Image Enhancement of Coronary Arteries Program and Detection and Quantification of Lesions in Deep-Lying Arteries and in Coronary Arteries Program. The approaches taken by these researchers can be broken into five broad categories, described below.

First, it is necessary to establish a definition of the most common electronic imaging system for looking at arteries in the body. The system consists of a rotating anode x-ray tube, broad-beam radiation geometry, and an image-intensifier television (II-TV) chain. The research being carried out under these programs is addressed in large part to the inadequacies of one or more of these three imaging system elements.

Approach 1. This group of investigators has chosen to keep the three standard imaging components intact and to apply computerized image processing techniques either to improve image quality or to extract accurate quantitative information. Mr. Robert Selzer and his colleagues at the Jet Propulsion Laboratory, California Institute of Technology, are processing cine angiograms with both spatial and temporal filtering techniques. Dr. Nelson and colleagues at the University of Utah are investigating temporal filtering schemes. Dr. Marcus and his group at the University of Iowa are applying videodensitometric techniques to quantitation of coronary lesions. Dr. Herman's group at the University of Pennsylvania is applying boundary methods to automating coronary videodensitometry.

The general agreement among these investigators is that: (1) The present imaging chain is inadequate for extracting accurate, consistent visualization of the coronary arteries via intravenous route of administration. (2) Intra-arterial applications are promising. Reduced contrast concentrations and the use of smaller catheters will be made possible by the various image enhancement techniques. (3) Using selective injections, there is a high likelihood that consistent, accurate quantitation of lesion severity will be possible, and perhaps a better assessment of lesion significance will follow from this knowledge.

Approach 2. This group of researchers has decided to alter the imaging geometry in some way to better isolate arteries in the body, specifically the coronary arteries. The approaches taken here include tomosynthesis, with and without energy subtraction, (Dr. Macovski and others, Stanford), computerized tomography, using the dynamic spatial reconstructor (DSR) (Dr. Ritman and others, Mayo Clinic), and a digital beam attenuator (DBA) (Dr. Mistretta, and colleagues, University of

Wisconsin). The DSR is at the most mature state of development. Replacement of the imaging chain promises to improve the signal-to-noise ratio severalfold. The ultimate effect on image performance will not be known without further testing, however. The tomosynthesis work is just beginning. Phantom images have been encouraging. The development of the DBA continues. Improvement in signal-to-noise has been demonstrated in the higher absorbing regions of an image. Animal and human studies await a faster method for fabricating the x-ray dodging filter.

Approach 3. Other groups of researchers (Dr. Sashin and colleagues, University of Pittsburgh, and Dr. Ovitt and others, University of Arizona) are replacing the detector in hopes of improving imaging performance. At the University of Arizona, the II-TV is being replaced by a proximity-focused II coupled via fiberoptics to multiple charge-coupled diode (CCD) arrays. Increased quantum efficiency and spatial resolution are expected. At the University of Pittsburgh, linear self-scanning diode arrays are being used in a slit-scanning device. Reasonably good images of a dog's proximal coronary artery segment have been made using IV injections of contrast. A dual-slit approach now is being investigated for coronary work. Testing of this dual-slit device is not yet complete.

Approach 4. A radical approach has been taken by Dr. Hofstadter and colleagues who are using a synchrotron as an x-ray source. Highly monoenergetic slit beams are formed that permit rapid energy switching between energies just above and below the K-shell absorption edge of iodine. A 2 cm-wide fan beam with 0.5 x 0.5 mm^2 resolution has been used for Kedge subtraction imaging of a dog's coronary arteries using IV administration of contrast material. Tissue and bone cancellation is almost perfect, leaving only high-contrast images of the iodine distribution. This technique has produced the best IV coronary angiograms so far by any researcher. Expansion of the system to a 15 cm-wide beam should permit human experimentation in the next year.

Approach 5. An obviously different approach is to use some probe other than x-rays to investigate the body's internal structures. Both B-scan ultrasound and nuclear magnetic resonance (NMR) are being used to image blood flow. Dr. Ralph Banes, Bowman Gray, reported on a high-resolution ultrasound technique that is being investigated for the characterization of atherosclerotic plaque in arteries close to the body surface, such as the carotids. Resolution of 50 to 100 microns was reported. Dr. Kaufman and others, University of California at San Francisco, are using NMR for imaging and quantitating blood flow in the body's major arteries, for example, vena cava, aorta. They are exploring the applications of NMR for imaging blood flow in smaller arteries as well, including the coronaries using a cardiac gating technique.

As is clear, research is progressing on a broad front. The next 3 years should determine which of these approaches is most useful. Depending on the nature of the desired diagnostic information, more than one technique may prove the "tool of choice."

II.

The common goal of these grants and contracts apparently is to develop methodology for assessment of coronary lesions with some degree of accuracy--say a 50 percent stenosis in a 2 mm-diameter artery--with the least degree of invasiveness possible. The candidates for minimal invasiveness include NMR and ultrasound, which do not require a catheter or injection of contrast media and do not subject the patient to ionizing radiation. Contrast arteriography with intravenous injection of the contrast is also included.

Other injection routes, "less invasive" than injection into the coronary ostia, which have some advantages over the IV route, have also been presented. For example, injection into the right ventricular outflow removes the right ventricle as an overlapping, contrast-filled, vascular structure. Injection to the aortic root or cusp likewise removes interference by the pulmonary vessels and left ventricle.

The Iowa group issued a precautionary note concerning the functional significance of percent stenosis as estimated by current standard methods. They found that the prestenotic segments used to compute percent stenosis may contain as much as one-third to one-half the amount of plaque as that in the stenotic segment. This group presented a videodensitometric method of assessing lesions that correlated reasonably well with anatomy as measured by the method of Brown and Dodge and also with peak blood velocity before and after reactive hyperemia; whereas, percent stenosis showed weak negative correlations with these parameters.

This videodensitometric method requires the operator to determine luminal center points above and below the stenosis and then to refine the computer estimate of the luminal edges. The Pennsylvania group described an approach to automated videodensitometry that was designed to reduce dependence on the operator, hence the operator's time, and thereby also, to increase reproducibility. This method proposes to use vessel tracking to locate arterial segments and "skeletonization" to link segments. Ambiguities resulting from overlapping vessels would be removed by the operator. Both of these methods might be useful to the other groups involved with contrast arteriography.

The fundamental problem that all methods attempt to solve is that of spatial resolution attended with or complicated by gross cardiac motion; overlapping contrast-filled vascular structures; noise in the form of x-ray scatter and veiling glare; and in some cases, artifact produced by the methodology itself. For further discussion purposes, we shall arbitrarily divide these methodologies into three categories:

1. Geometric dissection by tomographic approaches.
2. X-ray technology and devices.
3. Enhancement by computer processing.

It should be understood that differently categorized techniques may be functionally equivalent or very similar, for example, "masking," "filtering," and "subtraction."

1. Geometric dissection by tomographic approaches

These approaches include NMR, ultrasound, computerized axial tomography (CAT) scans (dynamic spatial reconstructor and multiple-view energy subtraction digital radiography), and the circular tomograph. A major advantage of these approaches is that when a three-dimensional (3-D) image has been constructed, the overlapping vascular structures, i.e., ventricles and pulmonary vessels, can be subtracted, leaving the coronary arterial tree alone to be visualized. Actually, the circular tomograph as proposed by the Utah group would dissect away image slices at the epicardial surface at various angles, so that the overlapping vascular structures would not be in the data. However, the means of 3-D reconstruction here is not as obvious as assembling parallel slices (NMR) or angular views (CAT scans).

A major problem of these approaches is that with current display systems, only one cross-section at a time can be viewed. This makes it difficult to view both stenotic and prestenotic segments unless they lie in the plane of the cross-section. This was a problem with NMR despite the ability to view coronal and sagittal as well as horizontal cross-sections. One approach would be to color code arteries as function of diameter and to project the results onto a 2-D display. However, unless the colors were somehow "natural" for the human interpreter, visual assessment might be difficult. Another possible approach would be to project sequential cross-sections onto a vibrating mirror. For flicker-free images, the mirror should cycle about 16 times per second. If the cycle length were about 10 cm, then the device would have to project 1,600 sequential frames/sec (on the average) on the mirror to obtain 1 mm spatial resolution; since the vibration of the mirror would presumably be sinusoidal, the peak rate would be 2,200-2,300 frames/sec. Thus, the spatial resolution of the vibrating mirror display would be limited by the rate at which the frames could be projected upon the mirror.

Another difficulty with tomographic approaches is preserving continuity of the arteries in the reconstruction of the 3-D image. One aspect of this problem involves how thick or thin the slices are (NMR) or how many angular views are taken (CAT scans). In either case, artifact can be generated by the process of assembling slices or angular views into a 3-D image.

Another aspect of this problem has to do with taking different slices or views from different heartbeats at the same phase of the cardiac cycle. At least as many beats are required as there are slices or views. If multiple points of the cardiac cycle are to be sampled, then even more beats will be required, depending upon the speed of acquiring individual frames. An image at maximum coronary filling during diastole would be most desirable.

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In putting together different parts of a heart image from different heartbeats, one assumes that the positional variation of the artery segments is negligible compared with the segment diameter. This is most likely to be valid at end-diastole, though respiration and patient restlessness could be a factor. At any other point in the cycle, especially in mid-diastole, variation will be affected by irregular heart rhythms. Variation could be reduced by averaging one slice/view at one phase for many beats, if necessary.

Considering the number of slices/views, the number of images per cardiac cycle, and the possibility of beat averaging, one is faced with significant requirements for storage as well as frame rate, which is a problem several speakers discussed.

2. X-ray technology and devices

Most of these devices deal with problems of noise associated with x-ray photon scatter in the subject or veiling glare in the image intensifiers. One method of treating scatter is by dual energy methods.

Broad-spectrum x-ray beams at 60 kpv and 120 kpv can be used to estimate scatter and to reduce it by subtraction or by synthesizing a cerium-oxide mask. Another approach would be to attenuate the energies of the 60 kvp beam above the iodine K-edge (33 kev) with a filter of some absorbing material such as ytterbium (K-edge at 61 kev).

The ultra-high-technology approach is the use of synchrotron radiation to produce high-intensity, monochromatic x-ray beams at 30 kvp (pre-edge) and 33 kpv (K-edge). This method achieves optimum cancellation of noniodine-filled structures, minimizes scatter, and hence gets a very high signal-to-noise ratio that is unobtainable with the broad-spectrum x-ray beams.

Another way to reduce scatter is to confine the x-ray source to a plane as close as possible and to use a linear detector in the same plane, thereby eliminating out-of-plane scatter, a method used by the Pittsburgh group and in the synchrotron project.

At the receptor end, x-ray collimators, increased thickness of receptor (cesium iodide), high-resolution image intensifiers, fiberoptic devices for windowing/focusing, and charge-couple devices have been employed to improve conversion efficiency, reduce scatter and/or glare, and enhance signal-to-noise ratio.

Some systems collect digital frames of 512 x 512 pixels and others 1,024 x 1,024. Dr. Mistretta suggests that the latter allows a 10 to 15 percent improvement in edge detection compared with the former, but a price must be paid in terms of increased storage requirements and decreased frame rates.

3. Enhancement by computer processing

As mentioned with tomography, positional variation of coronary segments may occur, even though images are taken at the exact same phase of the cardiac cycle of different beats. Hence, ECG-gated averaging is commonly used in nontomographic methods as well, to average out this variation (and any other noise that has a random temporal distribution), thereby enhancing the arterial image. Clearly, end-diastole at the R-wave is the most reliable point for beat averaging but not the most desirable. Other points, especially near mid-diastole, will be affected by irregular heart rhythms. Any beat with an abnormal contraction pattern, for example, PVC, should not be included in the average.

Several speakers also mentioned a sort of respiratory gating, either by suspending respiration in a controlled animal preparation or by taking images only during the resting phase of respiration, in some cases eliciting the cooperation of the patient to control his breathing pattern.

The remaining methods for computer enhancement include subtractive methods, filters, and intensity manipulations. Dual-energy subtraction to suppress nonvascular structures is discussed above. Another subtractive method would require several images during the passage of the bolus, so that those pixels that receive contrast earlier than the coronary arteries could be suppressed proportionately and selectively.

Another method took a weighted average of frames over seven points in time to serve as a subtractive mask. If coronary segments moved during that time, they would be blurred in the mask. If, however, they did not move, then they remained in the mask to be subtracted from the object image. This method was also very compute-heavy and was abandoned by the group at the California Institute of Technology.

This group has switched to a different method that shifts an image to the left of the coronary segment a distance equal to the diameter and in a direction orthogonal to the segment axis. Another image is shifted to the right in the same manner. The left-shift and right-shift images are averaged to form the subtractive mask.

A high-pass filter accomplishes much the same function as subtraction; by suppressing large-amplitude, low-spatial frequency variation, it enhances edges. Methods using a hybrid of low-pass filtering, temporal subtraction, and high-pass filtering were reported. Because these are presumably linear operations and hence commutative, the net effect of a high-pass and low-pass filter is a band-pass filter. If the spatial frequency bandwidth of the signal is known, a priori a band-pass filter could be implemented by convolution in the frequency domain with a hardware array processor, which would allow the filtering to be accomplished in real-time. This could be the nature of one of the real-time methods presented.

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All the methods above of course alter the intensity at individual pixels. Another method is the so-called median filter, which replaces the value of each pixel by the median value of the immediate 9-pixel neighborhood. This has a tendency to smooth the image without blurring it.

Histogram equalization applied globally or locally is another method that matches the dynamic range of the signal in the image to the available dynamic range of the display device, thereby enhancing visualization.

Another edge enhancer is the Laplacian, which has some similarity but not the specificity of the spatial-shift method described above.

Summary

The least invasive methods are ultrasound and NMR. Ultrasound imaging of the coronary arteries was the subject of an earlier session and is not discussed here.

NMR has so far shown only proximal segments of the coronary tree; how far distal this method can be carried seems problematical at this time, though its usefulness for grosser cardiac pathology has been well demonstrated.

The remaining projects dealt with contrast arteriography. Several reported using sophisticated phantoms, including insertion of plugs into a coronary model of known diameter and length and placement of a pig heart within a human cadaver chest cavity. Because the anatomy of phantoms can be accurately quantified, they are very useful for developing methodology. Nevertheless, several speakers expressed pessimism about the potential of IV contrast arteriography to achieve the desired spatial resolution or clinical usefulness. Certainly, most of the images that showed well-delineated coronary arteries were done with other injection sites, i.e., the right ventricular outflow tract, the aortic root, the aortic cusp, or the coronary ostia. While it is possible that some combination of the methodologies presented will approach the desired goal close enough to be clinically useful, the potential of such a combination has yet to be clearly demonstrated. Even so, the methodologies presented will find application in the assessment of grosser cardiac pathologies, and that is not an inconsiderable side benefit.

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ABSTRACTS
Calcification of Prosthetic Materials

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AMERICAN DENTAL ASSOCIATION HEALTH FOUNDATION
Prosthetic Materials in the Cardiovascular System
GRANT NUMBER: 5 R01 HL 30035-02

A serious need exists for a better understanding of the thermodynamic, kinetic, and structural factors governing a wide variety of biological calcifications, including those that occur in the arteriovenous system. We have made significant progress in all three of these areas. Equilibration techniques, originally developed for pure calcium phosphate systems, were applied to ultrafiltered serum and to the mineral in arteriosclerotic plaque. After equilibration of serum with $CaHPO_4.2H_2O$ (DCPD), $Ca_8H_2(PO_4)_6.5H_2O$ (OCP), or $Ca_5(PO_4)_3OH$ (OHAp), Ca and PO_4 concentrations and pH were measured, and the results were used to calculate the degrees of saturation of serum with respect to the above solids.

Native, ultrafiltered serum was found to be approximately saturated with respect to OCP, highly undersaturated with respect to DCPD, and highly supersaturated with respect to OHAp. Thus, OCP appears to establish the level of saturation of serum. Ultrafiltered serum was found to be essentially free of ions that complex Ca and PO_4. After prolonged equilibration of serum with DCPD, the level of saturation decreased to that of OCP, and x-ray diffraction of the solid phase revealed that it had transformed to OCP. After further equilibration, the solution composition approached saturation with respect to OHAp. This proves that the transformation sequence, DCPD-> OCP-> OHAp, can take place in serum.

These results, if confirmed by additional studies, establish the feasibility of OCP as a precursor in the formation of mineral on prosthetic devices in atherosclerotic plaque and in other passive pathological calcifications. Lipid-extracted, enzyme-treated plaque repeatedly equilibrated with acid revealed an apparent solubility equivalent to that of β-$Ca_3(PO_4)_2$.

The experimental techniques we have developed and the concepts we have derived from the results have application for the study of a wide range of pathological calcifications.

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UNIVERSITY OF PENNSYLVANIA
Calcification Mechanisms in Cardiovascular Prostheses
GRANT NUMBER: 5 R01 HL 29979-02

Calcification of bioprosthetic heart valves and artificial heart or assist-device bladders continues to limit progress in these fields. Our studies of calcification mechanisms include in vivo and in vitro methods. Cardiac patch grafts of glutaraldehyde-fixed bovine pericardium (Pc) were mounted on rigid epoxy rings and implanted as myocardial windows in the right atrium and right ventricle of young sheep. Excess portions of Pc obtained in trimming the implants were placed subcutaneously. Time course studies have demonstrated focal or diffuse thrombosis at 1 to 2 weeks but little or no thrombus in specimens left in for 4 weeks. After 2 weeks, mineral was often evident in low-energy soft tissue radiographs at necropsy but absent in antimortem fluoroscopy, radiographs, and computed axial tomography. Pc grafts processed and supplied in a phosphate-buffered system appeared to have more calcification than those processed in an acetate buffer. Light microscopy and scanning electron microscopy with energy dispersive x-ray spectrometry (EDX) show evidence of layering of mineral within the pericardium and also within the organizing thrombus that forms a pseudoneointima (PNI) on the blood-contacting surface.

In biochemical studies, Pc explants were analyzed for inorganic Ca and P, alkaline phosphatase activity, total protein, and lipid phosphorus. When considered as a function of implant time, it was found that the heterograft calcifies and that the calcification is time-dependent, although, in all samples analyzed, the pattern of calcification was irregular. Alkaline phosphatase activity in the explants was similar to that of serum for short implantations and then declined to about 10 percent of the initial value by 120 days of implantation. While deposits of phospholipids and proteins were detected, a mechanistic relationship between deposition of these materials and calcification could not be established.

In in vitro experiments, Pc patches were exposed to pulsatile stress in the presence of normal saline or sheep serum. Control patches were exposed to serum in a passive manner. Mineralization was scored using an analytical scheme similar to that used for the in vivo samples. The results of these experiments show that both stressed and passive exposure of the pericardium to serum could lead to the accumulation of ions, lipids, and proteins. The rate of accumulation was slow, with most components reaching maximum values in 1 to 3 hours. In some experiments, pumping stresses resulted in enhanced uptake of mineral ions.

Comparison of the proteins extracted from calcified explants with normal sheep serum revealed no pattern of selective protein adsorption.

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Irving M. Shapiro, B.D.S., Ph.D., Investigator (Biochemistry)
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MAYO CLINIC AND MAYO FOUNDATION
Quantification of Regional Platelet Thrombosis and Regional Calcium Mapping on Pericardial Tissue Valve Prosthesis With Diphosphonate Treatment in Calves
GRANT NUMBER: 5 R01 HL 28974-02

Ninety-five Holstein calves were implanted with 25 mm Ionescu-Shiley pericardial tissue valve prostheses in mitral annulus and two 2 cm x 2 cm glutaraldehyde-fixed pericardial patches under the skin in the abdomen. Calves in the control and diphosphonate-treated (DP) groups were killed at 1, 14, 30, and 90 days after valve-prosthesis implantation. In the treated group, diphosphonate solution was administered subcutaneously. Platelet thrombosis in the tissue valve components was noninvasively imaged with autologous Indium-111-labeled platelets, and after harvesting the valve and dissections, regional platelet thrombosis was quantified with Indium-111-labeled platelets. Twenty-four hours before killing, 700 to 800 μCi of $^{45}CaCl_2$ and 500 to 700 μCi of autologous Indium-111-labeled platelets were administered intravenously. Platelet and fibrinogen consumption were further quantified by platelet survival with Indium-111-platelets and ^{125}I-labeled bovine fibrinogen, respectively, at 7 days preoperation, immediately postoperation, and 14 and 45 days postimplantation.

After explantation, each leaflet was carefully separated from the sewing ring and mapped for regional platelet thrombosis and calcification. Total calcium in four zones of leaflets (figure 1) and the sewing ring was determined by atomic absorption spectrometry and was further checked by energy dispersive x-ray analysis (Ca P). Endothelial cell coverage of leaflets was monitored by scanning electron microscopic technique. Results of regional calcification in the control and DP-treated calves at 1, 14, 30, and 90 days postimplantation are shown in table 1.

Although the results indicate that DP treatment reduces calcification in all sections of leaflets at 90 days, the side effect (inhibition of bone growth) is severe enough to prevent its clinical trial. We have recently developed a new technique of processing collagenous tissue. This technique involves removal of antigenic proteins with detergents; immobilization of immunosuppressive drugs, including diphosphonate derivatives; stabilization of drug-collagen bond by borohydride reduction; and removal of excess glutaraldehyde before implantation. This processing of pericardial tissue promotes spontaneous endothelial cell coverage of the entire leaflet surface. Our preliminary granulocyte retention study with Indium-111-labeled granulocyte on leaflet surface also indicates that granulocyte infiltration is reduced due to this processing technique. This finding suggests that removal of antigenic

sites and immobilization of immunosuppressive drug reduce leukocyte infiltration, which is known to inhibit endothelial cell coverage of cardiovascular prostheses.

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Table 1. Time Course of Increase in Calcification by Regional Mapping of Calcium (μ/mg of wet tissue) in Leaflets of Control and Diphosphonate-Treated Calves Implanted With 25 mm Pericardial Tissue Valves

CONTROL CALVES

	1 Day (n=8)	14 Days (n=5)	30 Days (n=6)	90 Days (n=6)
Free Edge	0.11 ± 0.04	0.49 ± 0.57	2.63 ± 3.42	30.54 ± 29.99
Central Zone	0.11 ± 0.20	0.45 ± 0.43	1.38 ± 2.57	23.51 ± 14.17
Flexion Zone	0.16 ± 0.40	2.06 ± 1.96	3.34 ± 3.23	36.76 ± 20.22
Attachment Zone	0.13 ± 0.06	2.85 ± 2.55	10.73 ± 12.57	33.55 ± 20.19
Sewing Ring	0.74 ± 0.77	0.72 ± 0.42	0.68 ± 0.39	0.62 ± 0.37

DIPHOSPHONATE-TREATED CALVES

	1 Day (n=6)	14 Days (n=6)	30 Days (n=8)	90 Days (n=6)
Free Edge	0.15 ± 0.04	0.82 ± 0.42	7.33 ± 6.26	8.94 ± 14.51
Central Zone	0.14 ± 0.02	0.75 ± 0.50	4.53 ± 3.28	5.90 ± 7.24
Flexion Zone	0.23 ± 0.26	0.92 ± 0.56	2.95 ± 4.01	16.53 ± 21.20
Attachment Zone	0.11 ± 0.04	0.38 ± 0.35	1.43 ± 1.59	1.35 ± 1.69
Sewing Ring	0.17 ± 0.06	0.40 ± 0.31	0.35 ± 0.25	0.27 ± 0.19

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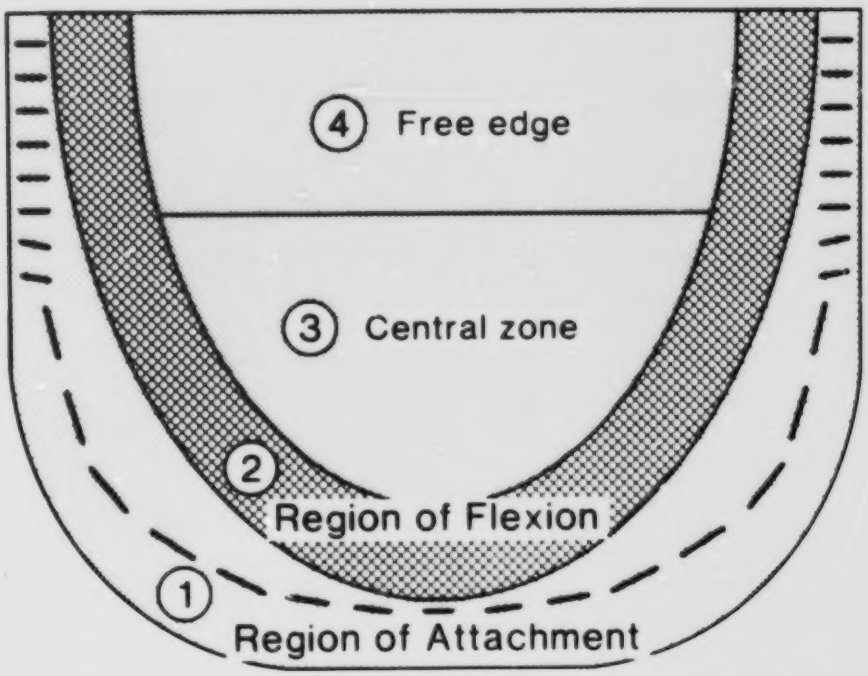

Figure 1. The four zones for mapping of calcification and thrombosis in each leaflet of tissue valve prosthesis implanted in calves.

MAYO CLINIC AND MAYO FOUNDATION
Quantification of Granulocyte Deposition on Vascular Grafts in Dogs with Indium-111-Labeled Granulocytes
GRANT NUMBER: 5 R01 HL 28974-02

A new radioisotopic technique has been developed for quantification of granulocyte deposition on vascular grafts. Nine healthy mongrel dogs underwent bilateral femoral implants with grafts of femoral vein and 4 mm Goretex. Pure granulocytes separated from whole blood by centrifugal elutriation were labeled with Indium-111-tropolone in plasma. Granulocyte harvesting efficiency was 25 ± 12 percent, and labeling efficiency was 87 ± 7 percent. Three hours postinjection of labeled granulocytes (282 ± 115) x 10^6 and 2 hours postreperfusion, the grafts were harvested and cut into several segments to study areas of anastomoses and midsections of grafts. From the radioactivity in blood and graft sections, area of graft sections, anastomoses and granulocyte counts, and differential white cell counts, the number of granulocytes adherent to a unit area of graft sections were calculated. These quantifications of granulocyte deposition indicate that midsections of Teflon graft retain more granulocytes (260 x $10^3/mm^2$) than midsections of vein grafts (20 x $10^3/mm^2$). Anastomoses of vein grafts retain more granulocytes (40 x $10^3/mm^2$) than midsections and vice versa for the Goretex grafts. A major fraction of granulocytes on Goretex grafts are incorporated into thrombus. Semiquantitative information obtained by scintigraphy of granulocyte deposition on vascular grafts with a computerized gamma camera also confirms this observation. This technique thus permits us to study granulocyte deposition on vascular grafts and the effect of granulocytes on inhibition of endothelial cell coverage of cardiovascular prostheses.

Mrinal K. Dewanjee, Ph.D., Principal Investigator
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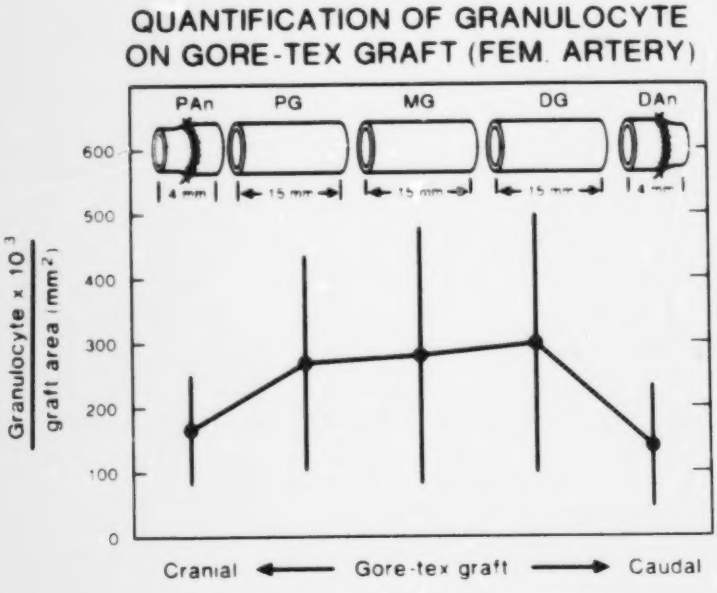

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THE CHILDREN'S HOSPITAL, BOSTON, MASSACHUSETTS
Structural Proteins in Bioprosthetic Valve Calcification
GRANT NUMBER: 5 R01 HL 32346-02

Collagen calcification is an important feature of the pathologic mineralization of bioprosthetic heart valves. In the second year of this program, research has focused on the following: (1) the events that precede and lead to collagen calcification in bioprosthetic heart valve calcification, (2) the fate of implants of purified type I collagen, and (3) the importance to calcification of residual aldehyde functions after glutaraldehyde pretreatment of collagenous implants.

Studies of the early events in bioprosthetic cusp subcutaneous implants (both bovine pericardial and porcine aortic) indicate that initial calcific deposits first appearing after 48 hours of implantation are predominantly associated with devitalized cell membrane structures. After 14 days, in both types of implants, collagen calcification and membrane-oriented deposits become equally prominent, eventually forming calcific nodules that destroy the cuspal integrity. The kinetics of both pericardial and aortic bioprosthetic implant calcification appear to be identical and plateau at peak levels after 60 days of subcutaneous implantation.

Subcutaneous implants of purified type I collagen, the principal collagen present in bioprosthetic cusps, calcify only if they are pretreated with aldehyde-based cross-linking reagents, either glutaraldehyde or formaldehyde (table 1). Nontreated collagen implants were completely resorbed without calcifying. It is of interest that the extent of calcification did not appear to be related to the duration of exposure to the cross-linking agents or the degree of cross-linking as determined by shrinkage temperature and collagenase digestibility. Studies of the importance to calcification of residual aldehyde groups remaining after glutaraldehyde pretreatment of collagen examined the covalent incorporation of aminohydroxydiphosphonate (APDP). It was hypothesized that residual aldehyde groups would form Schiff-base compounds with the amino function of APDP and that this bound diphosphonate might inhibit the events of collagen calcification. APDP pretreatment (0.14 M APDP, pH 7.4 for 24 hours) significantly inhibited collagen calcification (table 1) compared to control. Similar results were obtained by pretreating porcine aortic cusps with APDP. Future work in this program will further investigate the importance of the collagen-glutaraldehyde interaction, the effects of bound pharmacologic agents such as APDP, and the relationships during early crystal formation between collagen and other matrix components involved in the calcification process.

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Table 1. Calcification of Glutaraldehyde-Pretreated Collagen Implants

Experiment	N	Ca++(μg/mg)
Glutaraldehyde (Glut.) Pretreated	14	56.5 ± 6.3
Formaldehyde Pretreated	14	98.6 ± 5.4
Glut. Plus APDP*	10	1.8 ± 0.2
Porcine Aortic Cusp (PAC)	19	154.9 ± 4.1
PAC Plus APDP	10	24.2 ± 7.4

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ABIOMED (APPLIED BIOMEDICAL CORPORATION)
Mechanical Etiology of Calcification
GRANT NUMBER: 5 R01 HL 30013-02

Evidence in the literature strongly suggests a correlation between mechanical factors and intrinsic dystrophic calcification on prosthetic blood-contacting surfaces. The purpose of this study is to elucidate this connection using the calf as an accelerated model. Experiments involve fabrication, characterization, implantation, retrieval, and subsequent analyses of valved conduits whose surface morphology can be systematically varied and where the spatial distributions and quantitative levels of mechanical strain and fluid dynamic shearing stresses are known.

During the past year, there were 10 implants of left ventricle to aorta valved conduits (with ligation of the ascending aorta). Three were early surgical failures due primarily to inflow cannula misalignment. The remaining seven were terminated electively at gradually increasing implant durations of 27, 73, 106, 120, and 154 (three experiments) days. No anticoagulant or antithrombotic pharmacologic therapy was used. Except for the 120-day implant, the conduit surfaces and trileaflet valves were fabricated from smooth Angioflex polyurethane. The 120-day implant was identical except that a section of conduit distal to the trileaflet valve had a textured Angioflex surface. The valve leaflet thickness resulted in an 8 to 10 percent mechanical strain at the leaflet conduit junction.

Mean conduit flow ranged from 6 to 8 l/min at implantation to 11 to 15 l/min at termination of the longer implants. Thus, transient peak fluid dynamic shear stresses on the conduit surfaces distal to the trileaflet valve ranged from 800 dyn/cm^2 at implant to approximately 2,000 dyn/cm^2 at explant after 22 weeks. Peak fluid dynamic stresses on conduit surfaces proximal to the trileaflet valve ranged from 50 to 125 dyn/cm^2.

Hematological parameters were within normal limits for the calf model. Preoperative osteocalcin levels were much higher than adult human values (6 to 10 ng/dl). There were wide variations between different animals with values ranging from 25 ng/ml to 250 ng/ml. This variation may partially explain why wide variations in calcific deposits have been observed using this model.

Conduits explanted after 27, 73, and 106 days were devoid of calcification (examined by scanning electron microscopy/energy dispersive x-ray spectrometry (SEM/EDAX)). Conduits explanted after 120 and 154 days (three experiments) all showed calcification easily discerned by SEM/EDAX. The peak osteocalcin levels in the conduits with calcific deposits ranged from 138 to 187 ng/ml. The peak level for the 106-day noncalcified implant was 246 ng/ml.

At this time, observations on the nature and distribution of calcific deposits can be summarized as follows:

1. Two kinds of deposits have been observed on smooth surfaces.

   a. Gross, rough, "heavier" deposits are found on moving surfaces and appear to correlate with areas of mechanical strain. Some of these deposits could be visually observed.

   b. Flat plate-like "plaque" deposits are found on both moving and nonmoving surfaces. These deposits had very regular distinct shapes with very flat profiles (< 2 μm in height) and could be only observed by SEM. In some areas, these plaques grow to cover the surface with a flat layer.

2. The plaque deposits appear to be a surface phenomenon. They were not found in large surface defects (> 5-10 μm). However, there may be a correlation with submicron-scale surface morphology. They also appear to be precursors for the heavier deposits.

3. At this time, we do not have a quantitative measure of the amount of deposits and their correlation fluid shear stresses, but qualitatively, calcification appears heavier at areas of higher stresses.

4. The one experiment (120 days) with a textured conduit showed the heavier kind of calcification but only at the blood-contacting surface layer.

The major questions to be addressed by future work are the nature and genesis of the flat plaque deposits.

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THE CHILDREN'S HOSPITAL, HARVARD MEDICAL SCHOOL
Blood-Material Interactions: Calcification Considerations in Deposition and Degradation of Calcified Deposits in Cardiac Assist Devices
GRANT NUMBER: 5 R01 HL 32356-03

Microscopic observations of calcific deposits formed on textured Biomer surfaces of left ventricular assist devices that develop a pseudointimal (PI) matrix have revealed the following associations. Calcification is initiated at the polymer-PI junction and in discontinuous areas of the matrix due to poor adherence of the PI. The calcific deposits are hydroxyapatite and are prevalent on the flexing axes of the blood pump or any area of strain or decreased blood flow. Specific sites of calcification that have been identified include bacteria, plasma membrane of degenerated cells, intracellular vesicles of macrophages, and nuclei of giant cells, which predominate on Dacron-flocked fibril surfaces but not on Biomer fibrils.

Our studies have focused on the identification and role of specific calcium-binding proteins associated with the calcific deposits to understand fundamental mechanisms of mineral accretion in pathologic calcifications. We have identified serum proteins rich in plaques that are also accumulated in bone, albumin, α2glycoprotein, O-phosphoserine-containing proteins, and osteocalcin. A linear correlation of the vitamin K-dependent bone, osteocalcin, with calcium occurs in a variety of pathologic calcifications (inflammatory subcutaneous calcification, heart valves, kidney stones), including the blood pumps from anticoagulated cows. Although sodium warfarin inhibits synthesis of the γ-carboxyglutamic acid residues that promote calcium binding, the protein is rich in glutamic and aspartic acid and still has hydroxyapatite-binding potential. Certain physiologic circumstances dictate high circulating levels of the bone protein, such as in healthy rapid-growing young animals and children during sodium warfarin treatment.

Although osteocalcin is synthesized in concert with new bone formation and mineralization, we have just identified that its precise function is in the regulation of bone resorption. Synthesis is stimulated by $1,25(OH)_2D_3$, and bone that is deficient in osteocalcin is poorly resorbed in both in vivo and in vitro models. Osteocalcin and α2glycoprotein have chemoattractant activity for monocytes and macrophages and can stimulate phagocytosis. Thus, we now have an appreciation for a potentially beneficial role for certain proteins with affinity for hydroxyapatite. We are currently using these models to test the degradation of calcific deposits from cardiac assist devices and other pathologic deposits.

Jane B. Lian, Ph.D., Principal Investigator

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Small Vessel Prostheses

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TUFTS-NEW ENGLAND MEDICAL CENTER
Endothelial Cell Seeding of Small Vessel Prostheses
GRANT NUMBER: 5 RO1 HL 28855-03

The overall objective of this project is to determine the effect of endothelial cell seeding on the thrombogenicity and healing of small-caliber grafts in primates. Endothelial cells were enzymatically harvested from baboon cephalic veins and cultured in medium supplemented with fetal calf serum, bovine endothelial cell growth factor, and porcine heparin. Endothelial cells were characterized by morphology, immunochemistry, and prostacyclin production. Eight baboons received 17 knitted Dacron carotid interposition grafts in a paired-graft experiment. In addition, seven polytetrafluoroethylene (PTFE) grafts were implanted when the Dacron drafts were harvested. One graft of each pair was preclotted with blood containing media, the other with blood containing media with 3 to 7 x 10^6 autogenous endothelial cells. Platelets were isolated, labeled with Indium-111, and their accumulation on grafts monitored 24 hours after injection with static gamma camera scans at 24 hours, 2, 3, and 4 weeks postimplantation. Grafts were harvested at approximately 5 weeks postimplantation and examined using light and electron microscopy. Endothelial cell seeding significantly ($p < .05$) reduces the platelet reactivity of Dacron grafts 2 to 4 weeks after implantation, but the effect was small. When compared with paired control grafts, seeded grafts had a more cellular lining, less fibrin coagulum, and more endothelial cells lining the lumen. The thickness of the lining of control grafts was generally greater than that of seeded grafts due to the greater accumulation of fibrin coagulum and adherent blood cells. The lining of seeded PTFE grafts was significantly thinner than that of seeded Dacron grafts.

Allan D. Callow, M.D., Ph.D., Principal Investigator

INDIANA UNIVERSITY
Endothelial Seeding of Vascular Grafts
GRANT NUMBER: 2 RO1 HL 24247-01A1

Small artery prostheses with an extensive endothelial surface demonstrate better patency than unlined prostheses. Our efforts to line e-polytetrafluoroethylene (e-PTFE) and Dacron grafts with endothelium in tissue culture have met with only sporadic success. Polyester elastomer (PE) was tested for its capacity to serve as a tissue culture substrate and as a culture-lined graft. PE patches were coated with thin layers of gel, thrombin coagulated plasma, and plasma fibronectin. The coated and uncoated patches were inoculated with 43 to 51 cells/mm^2 of human umbilical vein endothelial cells and maintained in tissue culture for 7 to 11 days, while cell growth was analyzed by planimetry. Polystyrene tissue culture plates served as the control surface. There was no significant difference in the rate of cell multiplication or the maximum surface coverage (89 $\pm$ 9 percent) achieved on polystyrene tissue culture plates, bare or coated PE.

Tubes of PE were extruded, cut into segments measuring 4 mm ID and 60 mm in length, and inoculated with 10^6 endothelial cells labeled with Indium-111 18 hours before testing. The tubes were subjected to gamma camera analysis just before and 60 minutes after implantation in dog carotid arteries. Four dogs (group I) received allogeneic canine cells. Group II (N = 4) received human umbilical cells, and group III (I.C. = 7) received autogenous cells. Initial cell attachment was 55 percent in group I, 52 percent in group II, and 78 percent in group III. Cell retention after perfusion was 15 percent in group I, 27 percent in group II, and 22 percent in group III. None of these differences was significant.

We conclude that PE is a polymer that supports tissue-cultured endothelium, that large percentages of the PE-cultured surface can be covered with various types of endothelium within 18 hours of inoculation, and that early losses of cultured cells from PE during in vivo arterial perfusion are caused by other than immune reactions. Future efforts will include an analysis of the causes of early cell loss from the PE surface during in vivo perfusion and attempts to improve the endothelial-PE bond.

John Glover, M.D., Principal Investigator
Malcolm Herring, M.D., Collaborating Investigator

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MASSACHUSETTS GENERAL HOSPITAL AND HARVARD MEDICAL SCHOOL
Effects of Compliance Mismatch in Arterial Grafts
GRANT NUMBER: 5 R01 HL 29429-03

The objective of this project is to conclusively demonstrate or rule out compliance as a significant influence on graft patency. This is to be accomplished by comparing grafts that have different mechanical properties but identical flow surfaces.

Using a technique of differential fixation with glutaraldehyde, we produced two conduits of equivalent surfaces, as determined by scanning electron microscopy and measurements of critical surface tension and infrared spectroscopy. Their mechanical properties were significantly different, with circumferential compliance being equivalent to either the native artery or synthetic grafts (e.g., polytetrafluoroethylene). These conduits were inserted bilaterally in the femoral artery of dogs, resulting in 100 percent patency for the compliant graft only. Histologically, some stiff grafts were found to contain longitudinal cracks within their walls. Whether these cracks protrude to the lumenal surface and are thus responsible for thrombosis in these grafts must be determined before these data are accepted as proof of the compliance hypothesis. Further histological evaluation of the glutaraldehyde fixation model is under way.

Following up on our demonstration of perianastomotic hyperplasia (PHZ), wherein the compliance of artery increases then drops to a minimum as one approaches an anastomotic suture line, we have explored the incidence and possible causes of PHZ. We found PHZ in 18 of 21 continuous anastomoses (CON) and 8 of 16 interrupted anastomoses (INT). Despite its greater incidence in CON, the magnitude of the peak compliance, relative to control artery, was equivalent with both suture techniques. Changes in vessel diameter, longitudinal tension, and anastomotic compliance have been examined as possible contributors to PHZ; however, its direct cause is still unclear. PHZ produces a local mismatch in compliance at the suture line. It has been observed with equal frequency in the presence of compliant and stiff grafts, suggesting that even with a graft of optimal compliance, there may be an influence of compliance mismatch. The possible relationship between PHZ and subintimal hyperplasia at the anastomoses, a cause of frequent graft failure, is being explored.

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COLUMBIA UNIVERSITY AND
HINES VETERANS ADMINISTRATION HOSPITAL
Application of Arterial Regeneration
GRANT NUMBERS: 1 RO1 HL 29268-02 and 5 RO1 HL 32340-02

The clinical efficacy of small vessel prostheses is largely determined by the morphologic and functional characteristics of its elicited cellular reactions.

Interposition of woven absorbable polyglycolic acid (P prostheses, 3.5 mm ID x 24 mm length, into adult rabbit aortas was followed after 7 days by its phagocytosis by macrophages. At 2 weeks, ultrastructurally primitive mesenchymal cells transgressed the interstices, proliferated for 2 weeks, and differentiated for 3 months into myofibroblasts. Those nearer the lumen showed greater smooth muscle characteristics, while those more peripherally located were progressively more fibroblast-like. A confluent endothelial-like flow surface was present after 2 weeks. Sonomicrometric diameter versus pressure relationships of explanted PGA-induced regenerated vessels showed elastic characteristics resembling normal arteries. These specimens withstood pulsatile saline infusion to 4,000 mm Hg systolic and 1,200 mm Hg mean pressures. Similarly woven Dacron prostheses elicited a significantly thinner, less-cellular reaction with a fibrinous flow surface.

Several compound prostheses of absorbable PGA or polyglactin 910 (PG910) interwoven with or surrounded by Dacron demonstrated both a stimulation of transinterstitial cellular migration by the absorbable polymer and an inhibition of migration by even small Dacron concentrations. Inner capsular myofibroblast deposition within 100 percent PGA or PG910 was more extensive than within Dacron-containing compound prostheses and, in time, exceeded that within 100 percent Dacron prostheses.

Polydioxanone (PDS) prostheses stimulated a transinterstitial cellular regeneration identical to PGA but developing more slowly. Myofibroblast migration and proliferation again coincided with macrophage phagocytosis of the prosthetic material.

Results suggest a multifactorial interaction between the prosthesis and its elicited transinterstitial cellular regeneration, which may include a differential induction of macrophage-derived growth factor activity.

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UNIVERSITY OF ARIZONA
Small Diameter Vascular Prostheses
GRANT NUMBER: 5 R01 HL 29164-03

Vascular grafts composed of acellular vascular matrix (AVM) are prepared by sequential extraction of native vessels (e.g., carotid arteries) with nonionic and ionic detergents. The resulting material (AVM) is free of cells, nuclei, and phospholipids. AVM grafts of 3 to 4 mm ID and 10 to 15 cm length implanted for 18 months in the carotid position of dogs remain fully patent and thrombus free. This report presents our observations on the process of neointima formation in AVM grafts implanted in the carotid position in dogs.

The rate of recellularization of the luminal surface of implanted AVM was measured by infusion of a solution of Evans Blue 2 hours prior to sacrifice. Nonrecellularized AVM surface areas stain intensely blue, while the recellularized areas exclude the dye and remain unstained. The validity of dye exclusion as an indicator of recellularization was confirmed by light and scanning electron microscopy. Recellularization appears to proceed only from the anastomoses, with no evidence of insular recellularization at sites distant from the anastomoses. The degree of recellularization was measured at 1, 3, and 18 months. The rate of recellularization was approximately twice as fast from the proximal anastomosis than from the distal. Based on the 1- and 3-month observations, the proximal rates of recellularization were in the order of 0.9 cm a month, indicating that 15 cm grafts should be fully recellularized in approximately 10 months, and indeed, 18-month explants were completely recellularized.

The recellularized surface consists of a thin but multilayered pannus at each of the anastomoses, which rapidly thins to a single cell layer within approximately 1 cm. The cells of the monolayer and the luminal layer of cells over the pannus were positive for factor VIII antigen as indicated by immunohistology, demonstrating that full endothelial coverage was achieved. The neointimal cells appear to be strictly of luminal origin as there was no evidence of cells migrating to the luminal surface from the adventitia. Host cells do invade both the adventitia and the layers of the media directly adjoining the adventitia, but the compact elastin layers of the subluminal medial region remain free of host cells. The results described above were obtained with noncross-linked AVM. Preliminary evidence indicates that glutaraldehyde fixation severely inhibits formation of the neointima.

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SCRIPPS CLINIC AND RESEARCH FOUNDATION
Graft Thrombus Formation in Baboons
GRANT NUMBER: 5 R01 HL 31469-02

We have examined the effects of changes in platelet age, count, and prior exposure to thrombogenic surfaces with respect to arterial thrombus formation in baboons. In this model, thrombus formation was initiated by Dacron vascular grafts (4 mm x 10 cm) inserted as extension segments into chronic arteriovenous Silastic shunts. Following platelet labeling with Indium-111-oxine, platelet deposition was measured for 1 hour following blood contact under arterial flow conditions using a scintillation camera. In six animals, platelet deposition was assessed serially using fresh grafts inserted for 1 hour daily on 4 sequential days. Platelet deposition was equivalent on all grafts, rapidly increasing 30- to 50-fold and plateauing by 1 hour. All grafts produced equivalent reductions in circulating platelet count and blood Indium-111-platelet radioactivity, demonstrating that the labeled cells were functionally equivalent to the total platelet population. Between periods of graft placement, the remaining platelets survived normally. Platelet destruction by the graft produced a tenfold increase in plasma levels of platelet factor 4 (PF4) and β-thromboglobulin (βTG) but did not modify either the α-granule (PF4, βTG) or dense granule (adenosine diphosphate (ADP), adenosine triphosphate (ATP)) contents of circulating platelets. Total platelet deposition exhibited a second-order dependence upon the circulating platelet concentration, such that a doubling in platelet count between animals produced nearly a fourfold increase in platelet deposition. Heparin anticoagulation (100 U/kg and 1,000/kg) did not affect the extent of initial platelet deposition, although the higher dose reduced maximum platelet deposition by approximately 50 percent. We conclude that whereas the capacity of platelets to participate in arterial thrombus formation may be altered by antithrombotic therapy, it is not modified by either aging in the circulation or repeated acute exposure to thrombogenic surfaces.

We have also compared the relative capacities and mechanisms of aspirin, dipyridamole, sulfinpyrazone, and dazoxiben to prevent arterial thromboembolism in a baboon model. In 136 studies, the agents were given twice daily by oral administration both singly and in combination. The antithrombotic efficacy of a given therapy was determined by its capacity to interrupt steady-state platelet utilization induced by thrombogenic arteriovenous cannulae (Biomer polyurethane, 4 mm x 50 cm). When given alone, dipyridamole and sulfinpyrazone reduced the rate at which platelets were used by thrombus formation in a dose-dependent manner with essentially complete interruption by dipyridamole at 10 mg/kg/d. In contrast, neither aspirin (2 to 100 mg/kg/d) nor dazoxiben (20 to 100 mg/kg/d) decreased cannula platelet consumption detectably, despite the striking reduction in the capacity of platelets to produce thromboxane B_2. However, aspirin, but not dazoxiben, potentiated the antithrombotic effects of dipyridamole and sulfinpyrazone in a dose-dependent fashion without changing the pharmacokinetics for any

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of the agents. Complete potentiation required aspirin at 20 mg/kg/d to be given with each dose of dipyridamole. Since dazoxiben's blockade of platelet thromboxane A_2 production was not associated with antithrombotic potentiation, and since complete potentiation by aspirin required a dose that fully inhibited vascular production of prostacyclin (PGI_2), we conclude that aspirin's potentiating effect on dipyridamole is independent of PGI_2 production or inhibition of thromboxane A_2 formation. In addition, since frequent repeated and synchronous dosing of aspirin was necessary, aspirin's potentiating effects appear to be produced by mechanisms unrelated to its potent, irreversible inhibition of platelet cyclo-oxygenase.

Stephen R. Hanson, Ph.D., Principal Investigator
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BROWN UNIVERSITY
Bioresorbable Vascular Grafts
GRANT NUMBER: 1 R01 HL 28975-01A1

Our research hypotheses are that the biological elements of an arterial wall can be reorganized through the natural repair processes that occur in the slowly disappearing scaffold of a bioresorbable vascular graft and that these repair processes may provide a newly formed vessel of appropriate structural strength, elasticity, and hemocompatibility. The goals of this project are to fabricate and to evaluate vascular prostheses made of bioresorbable polymers.

There are four specific aims for the coming year:

1. To continue experiments with subcutaneous and vascular implants made of "triple ply" Vicryl (a 9:1 polyglycolic acid--poly(D, L-lactic acid) random copolymer) overcoated with a 1:1 composite of poly(D,L-lactic acid) and poly(2,3-butylene fumarate). This project involves subcutaneous implants in mice for the screening of polymer coatings and infrarenal aortic implants of tubular conduits in dogs for evaluation of durability and repair processes.

2. To continue the evaluation of existing and novel homo- and copolyesters of Krebs-cycle dicarboxylic acids as well as composites capable of delaying the rate of in vivo disintegration of standard bioresorbable polyesters. This project calls for polymer synthesis, fabrication of subcutaneous implants (mice), and retrieval at given intervals for molecular weight determinations and assessment of tissue reaction.

3. To fabricate vascular grafts woven from a continuous thread of 5-0 Vicryl and control grafts similarly woven of 220 denier, medical-grade Dacron. These prostheses will be coated with resorption-delaying polyesters selected through project 2.

4. To evaluate woven, coated bioresorbable vascular grafts implanted in the infrarenal aortic position in the dog and in the carotid position in the sheep (with the controlateral artery serving for implantation of a control Dacron graft). Polymer decay will be evaluated by gel permeation chromatography; tissue reaction will be evaluated by histology, histochemistry, electron microscopy, and characterization of the mechanical properties of the tissue capsule.

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Biomaterials

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UNIVERSITY OF AKRON
Physical Testing of Polymers for Use in Circulatory Assist Devices
CONTRACT NUMBER: NO1-HV-02909

Short-term fatigue tests were developed to evaluate alternate elastomers for use in the rubber diaphragms of blood pumps. This research was conducted primarily at Monsanto Research Corporation (now the Dayton Laboratory of Monsanto Company) and is continuing at the University of Akron. An experimental protocol has been developed to enable the comparison of the fatigue life of newer, developmental elastomers to other research elastomers and to the presently used cardiovascular elastomers. The test procedures can be conducted using relatively inexpensive commercially available fatigue testers for most of the tests. The results of these tests should be predictive for constant displacement fatigue applications, such as pusher-plate blood pumps.

The following test was found to have the highest correlation with both longer term in vitro fatigue tests and also to give results consistent with the limited long-term in vivo end-use device test results that are available. The test uses 5-inch American Society for Te ting Materials (ASTM) dog bone specimens with a 1 mm razor blade cut in the side. The specimens are fatigued at 2 Hz in 37° C air. (Many different environments were tested in this program, but air was found to correlate reasonably well with the whole human blood test results.) The test starts with a 1 percent strain on the samples. After each 24 hours, the strain is increased by 1 percent. The average strain at failure for each material is used to compare the fatigue life of the elastomers.

The reasons this test gives predictive results include the following: (1) A low strain, comparable to end-use applications, is used. Thus, the fatigue failure mechanism in this test is more likely the same mechanism occurring in the final product. (2) Starting with a low strain and increasing the strain allows any "coaxing effect" to occur. (The coaxing effect is primarily seen in metals, where preliminary fatigue at a lower stress increases the ultimate fatigue life at the higher stress.) (3) The average strain at failure is a measure of fatigue life that approximates the critical tearing energy to propagate a crack in fatigue (not to be confused with dynamic tear tests).

A second measure of fatigue life can be obtained using the same test without the starting cut. (Start at 50 percent strain, and increase the strain by 5 percent each day.) Although not as predictive as the above test, this test can provide additional information that may be useful for homogeneous elastomers in applications in the absence of stress concentrators.

Carl R. McMillin, Ph.D., Principal Investigator

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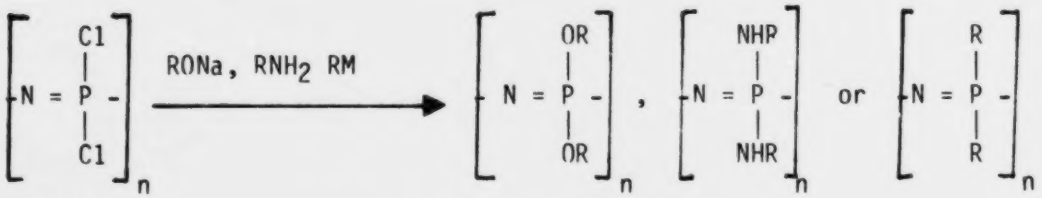
THE PENNSYLVANIA STATE UNIVERSITY
Poly(organophosphazenes) for Biomedical Uses
GRANT NUMBER: 5 R01 HL 11418-15

The use of synthetic polymers to solve biomedical problems is an important and growing part of biotechnology. Our objective is to pioneer new synthesis methods that will lead to entirely new polymers of special interest in biomedicine. These fall into two groups: biostable polymers that will be inert in a living system and bioactive polymers that can be used to mediate biochemical reactions or facilitate the delivery of chemotherapeutic agents.

Our synthetic approach is unusual. It makes use of a reactive inorganic high polymer (I) as a substrate for reactions with a wide range of organic reagents to generate high polymers with diverse properties that depend on the organic side group introduced.



I

(R = alkyl or aryl)

Subsequent chemistry carried out on the organic side groups allows further modification of the properties. Specific side groups (amino acid esters or imidazolyl) stimulate hydrolytic breakdown of the polymer and yield candidate materials for bioerodable, slow-release systems. Other side groups (CF_3CH_2O or C_6H_5O) confer biostability and bioinertness character.

In recent work, we have extended the boundaries of this field into the immobilization of catecholamines, steroids, antibacterial agents, and enzymes and have begun to examine the utility of these polymers as membranes for use in biomedical devices.

Harry R. Allcock, Ph.D., Principal Investigator

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WASHINGTON UNIVERSITY
Erythrocyte Deformability and Vascular Pathophysiology
GRANT NUMBER: 5 R01 HL 12839-15

Erythrocyte deformability is believed to be an important factor in microvascular function and is being widely investigated under both static and dynamic conditions. The overall objective of this project is to extend current knowledge of the deformability of normal and diseased erythrocytes with emphasis on those properties that govern the individual cell's capacity to change shape in response to rapidly varying flow patterns. Of particular interest are the physical and chemical changes in erythrocytes that may result in their sequestration in the spleen and other organs in vivo.

The experimental approach is to subject age-fractionated populations of normal and diseased cells to well-defined shear flows in the rheoscope, a viscometric device consisting of counter-rotating cone and plate. By means of still photography and videotaping, the steady state motion and deformation of the cells are recorded and also their shape recovery following abrupt flow cessation. These observations are being coupled with appropriate mathematical models in an effort to compute elastic and viscous moduli of the erythrocyte membrane. Simultaneous physical and chemical assays (mean cell volume and hemoglobin concentration, membrane phospholipid and protein, glycosylation, etc.) are carried out in a search for correlates of impaired deformability.

Current investigations are focused on erythrocytes from people with diabetes in poor metabolic control and with proliferative retinopathy, erythrocytes parasitized by different strains of malaria (Plasmodium berghei and cynomolgi) and by Babesia, erythrocytes from hypercholesteremic rabbits, and erythrocytes from humans with glucose-6-phosphate dehydrogenase deficiency. In parallel with the rheoscope studies, determinations of in vivo sequestration in the spleen and other organs of the rat are being examined as a means of verifying physiologic significance of in vitro indications of impaired deformability.

S. P. Sutera, Ph.D., Principal Investigator
R. A. Gardner, Ph.D., Project Leader
J. R. Williamson, M.D., Project Leader

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RICE UNIVERSITY
Flow Effects on Leukocyte Function and Surface Adhesion
GRANT NUMBER: 5 R01 HL 17437-09

The objectives of this research project remain to quantify the effects of mechanical forces on each of the various populations of leukocytes and to examine biochemical modification of these functional alterations. In addition, using a direct video microscopy visualization technique, we plan to examine flow effects on leukocyte adhesion to surfaces coated with purified proteins and endothelial or smooth muscle cells. The biochemical control mechanism of this process is also being investigated.

The development of delayed coagulation abnormalities after surgery is a significant clinical problem. One possible cause is expression of monocyte tissue factor activity (TFA), stimulated by mechanical trauma or artificial surface interaction. In this study, leukocytes and separated leukocyte fractions were exposed to controlled mechanical trauma in vitro, which in turn caused TFA generation in certain of the sheared samples. The presence of lymphocytes appeared to be necessary for the direct shear stress-induced expression of TFA. However, all sheared cells retained their viability and ability to produce TFA because if stimulated with endotoxin, significant TFA was assayed. Furthermore, at shear stresses comparable to those found in extracorporeal circulation and in artificial heart valves, significant leukocyte TFA could be induced 24 hours after the mechanical trauma exposure. In addition, this study supports the conclusions of other investigators of a lymphocyte-dependent pathway and a lymphocyte-independent pathway for TFA production by monocytes.

A modified Couette viscometer was used to study the effect of shear stresses on human lymphocyte function, including proliferative responses to phytohemagglutinin-P (PHA-P), interleukin-2 (IL-2) synthesis, cell viability, cellular enlargement, and cell density. Shear stress levels investigated were similar in magnitude to those found in blood pumps and dialysis units. At shear stress levels of 100 and 200 dyn/cm^2 for 10 minutes, a portion of the mononuclear cell suspension was lethally damaged. Shear stressed cells when cultured at 1×10^6 cells/ml did not incorporate significant amounts of thymidine into their deoxyribonucleic acid (DNA) nor synthesize detectable levels of IL-2. They also did not exhibit the characteristic cellular enlargement induced by PHA. In contrast, however, when the shear stressed cells were cultured at decreased cell densities of 0.5×10^6 and 0.25×10^6 cells/ml, they incorporated significantly greater amounts of thymidine along with a concomitant increase in synthesis of IL-2. The data suggest that a fraction of cells were shear stress damaged and that such damage inhibited the proliferation of the other cells in a density-dependent manner.

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The flow chamber for surface/leukocyte interaction visualization, with surfaces coated with either specific proteins or endothelial cells, is placed on a temperature-controlled epifluorescent microscope stage. It is then connected to a constant head flow loop. This system is a constant pressure drop loop, with a variable resistance to introduce pulsatility, if desired. The volumetric flow rate is determined by the height of the upper reservoir above the stage and is directly measured with an electromagnetic flowmeter. The upper reservoir has two outlets, one to the flow chamber and an overflow bypass directly to the lower reservoir. The flow from the return line (through the roller pump) is maintained slightly greater than the flow through the chamber, always assuring some overflow in the upper reservoir and thus a constant pressure drop across the flow chamber. The volume of the loop has been made as small as 8 ml. Experiments can be run on time scales of minutes or hours. Events are recorded on videotape using a video camera with image intensifier, either in real time or using a time-lapse video recorder.

To visualize leukocyte-vessel wall interactions in whole blood, the polymorphonuclear neutrophil leukocytes (PMNL) were labeled and epifluorescent video microscopy employed. The antimalarial drug quinacrine dihydrochloride (Quin) was used as the fluorescent label. It is actively taken up into PMNL granules and does not label the nuclear material. Labeling concentrations are 1 to 10 μM. At these concentrations, Quin does not affect PMNL chemiluminescence, chemotaxis, adherence to nylon fibers, or granule release. The excitation wave length is 440 nm with an emission maximum of 505 nm, allowing the use of standard fluorescein isothiocyanate (FITC) filters if necessary. Labeling of erythrocytes is negligible at these concentrations, or at least any fluorescence from red cells is quenched by intracellular hemoglobin. Interestingly, Quin does label the nucleus of lymphocytes, allowing their visualization if desired. If excess Quin is used, endothelial cells will also become fluorescent.

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Suzanne G. Eskin, Ph.D., Collaborating Investigator
Bill Brinkley, Ph.D., Collaborating Investigator

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UNIVERSITY OF UTAH
Initial Events in Thrombus Formation on Surfaces
GRANT NUMBER: 2 R01 HL 17623-11

It was shown that albumin-heparin conjugate has heparin-like activity as determined by activated partial thromboplastin time (APTT), factor Xa, and thrombin time assays. After precoating polymers with albumin-heparin conjugates, a strong prolongation of both the plasma recalcification time and whole blood clotting time was observed, indicating that surface-induced coagulation is inhibited. Although some release of the conjugate occurs, it was found that the adsorbed albumin-heparin conjugate caused prolonged clotting times and that its activity, like heparin in solution, is dependent on complex formation with antithrombin III (ATIII).

Besides surfaces-induced coagulation, platelet adhesion is being evaluated using ex vivo cells. The results indicate that albumin-heparin conjugate preadsorbed surfaces reduced initial blood platelet adhesion. This suggests that an albumin-heparin conjugate can be used for the improvement of the intrinsic blood compatibility of all kinds of materials that are used in contact with blood. Less platelet adhesion was observed when the surface was coated with the conjugate of albumin-low-molecular-weight, high-ATIII-affinity heparin.

In addition, basic studies on heparin binding to fibrinogen and fibronectin are being carried out using various fractions of heparin separated in this laboratory. Heparin-albumin conjugates and heparin-bound fibronectin are utilized for their adsorption onto polymer surfaces.

The ex vivo shunt experiments are under way to evaluate the adsorbed albumin-heparin conjugate contacting with whole rabbit blood.

Sung Wan Kim, Ph.D., Principal Investigator
Jan Feijen, Ph.D., Coinvestigator
Teruo Okano, Ph.D., Coinvestigator

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UNIVERSITY OF WASHINGTON
Cell and Protein Reaction With Foreign Materials
GRANT NUMBER: 5 R01 HL 19419-09

The work performed on this project since the original proposal was submitted has largely focused on the behavior of fibroblasts, macrophages, and platelets on solid surfaces in relation to the adsorption (from complex, relevant media) of certain proteins thought to influence this behavior (fibronectin, immunoglobulin G (IgG), fibrinogen, and von Willebrand's factor (VWF)). We have been able to show a linear correlation between the amount of fibronectin adsorbed from serum to surfaces and the spreading of 3T3 cells, even though the amount of adsorption and spreading varies greatly and in nonlinear, peculiar ways among the various surfaces and serum concentrations used.

A new way to perturb the adsorbed layer, variation in the serum or plasma concentration, has been demonstrated. This "mass action" effect is particularly useful for our cell studies because the resultant adsorption of the proteins is not linearly dependent on the concentration but instead passes through a maximum whose position depends on the type of protein, the type of surface, and the overall concentration of the complex mixture (serum or plasma) in characteristic and reproducible ways. Since the cellular response to surfaces treated with varying serum or plasma concentration may also pass through a maximum or assume some particular shape at the same conditions seen for a particular protein, we can probably conclude that the cell is, in fact, being controlled by the adsorbed amounts of that particular protein. This has been observed for 3T3 cells and fibronectin, and we are now working on the macrophage-IgG/complement C3 and platelet-fibrinogen/VWF systems to ascertain the generality of this phenomena. If it is seen in these diverse systems, the major hypothesis of this work, that the organization of the adsorbed layer dictated by the surface properties of a material dictates cellular response, will have been established. This demonstration would provide strong evidence for a central mechanism in the response of tissue to foreign surfaces. Since the rational design of improved biomaterials awaits any insight into mechanisms involved in cell-surface interactions, the work here may prove highly significant.

Complement activation studies begun before the current period have also been completed and show a correlation between complement activation and hydroxyethylmethacrylate (HEMA) content in the HEMA-EMA copolymer series. We have incidentally discovered a way to greatly enhance fibronectin adsorption with a rather simple and generally applicable technique, namely plasma discharge treatment in the presence of ethylene oxide. This may prove useful in modifying the surface regions of implants to enhance growth and "healing in" of the surrounding tissue (e.g., vascular grafts).

Thomas A. Horbett, Ph.D., Principal Investigator
Buddy D. Ratner, Ph.D., Investigator
Allan S. Hoffman, Sc.D., Investigator

UNIVERSITY OF UTAH
Novel Approach to Nonthrombogenic Polymer Surfaces
GRANT NUMBER: 5 R01 HL 20251-08

The immobilization of heparin using alkyl spacer arms was carried out to optimize yield on polyurethane surfaces. Heparin-releasing polyurethane was also studied to compare its biological activity with the immobilized system.

Immobilized heparin retained its ability to bind and inactivate thrombin and factor Xa. It was verified that such activity cannot be attributed to the leakage of bound heparin.

Heparin-immobilized polyurethane catheters implanted in canine femoral and jugular veins for 1-hour periods exhibited significant reduction in thrombus formation compared with untreated polyurethane contralateral controls. The catheters coated with a 9 percent heparin dispersion in polyurethane were capable of releasing active heparin for several hours, providing even greater improvement in antithrombogenicity. Both types of heparinized surface displayed reduced platelet aggregation and fibrin formation, although platelet adhesion was somewhat higher on the heparin-immobilized material than on the heparin-releasing surface.

A dual pharmacological approach to prevent thrombus formation and prevent platelet aggregation was achieved by directly coupling PGE_1 to heparin. The mixed anhydride method was performed using C^{14}-PGF_{2a} as a model. Elution profiles on gel permeation chromatography columns showed coupling of PGF_{2a} onto heparin to the extent of 4×10^{-8} moles PGF_{2a} per milligram heparin (14.2 μgm PGF_{2a}/mg heparin). Studies were performed to assure that PGF_{2a} was covalently bound to heparin, rather than physical adsorption (leakage studies).

PGE_1 was attached to heparin, based on the results of the pilot C^{14}-PGF_{2a} studies. Preliminary studies (in vitro) indicate the complex will be able to prevent thrombus formation, based on activated partial thromboplastin time (APTT) studies, and to prevent adenosine phosphate-induced platelet aggregation (rabbit model).

Sung Wan Kim, Ph.D., Principal Investigator
Teruo Okano, Ph.D., Coinvestigator

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BOSTON UNIVERSITY MEDICAL CENTER
Hemodynamics in Vascular Surgery
GRANT NUMBER: 5 R01 HL 21796-07

Failure of prosthetic arterial grafts usually occurs between 1 and 18 months following implantation. Early studies demonstrated that hyperplasia occurs at the anastomosis between the prosthetic graft and the host artery. However, the precise role of anastomotic hyperplasia in graft failure has not been delineated.

We have studied the fate of prosthetic arterial grafts in the dog model. Quantitative analysis showed that anastomotic hyperplasia occurred at both the proximal (upstream) and distal (downstream) anastomoses. In our model, there was significantly greater hyperplasia at the downstream anastomosis, where it was the cause of all delayed Dacron-graft failures. The primary localizing factor appears to be the downstream location. We constructed in vitro plastic models to study the flow disturbances at proximal and distal anastomoses. A comparison of those studies with our in vivo results indicates that flow disturbances, especially boundary layer separation, appear to play only a minor role in the development of anastomotic hyperplasia.

We hypothesize that downstream anastomotic hyperplasia is a result of contact activation of blood by the artificial surface, perhaps involving the release of platelet-derived growth factor. We have investigated this by placing long Dacron arterial grafts in dogs. Blood samples drawn across the length of the graft demonstrate a measurable increase in thromboxane B2 (TXB2) and fibrinopeptide A (FPA). Release of these substances is most marked immediately after placement of the Dacron graft. By 7 days, it has decreased markedly and remains stable thereafter. Flow reduction caused a marked increase in the release of TXB2 and FPA, and there appears to be a critical flow rate that triggers this release.

Further studies will be directed at comparing different prosthetic graft materials in terms of their propensity to develop downstream anastomotic hyperplasia and to cause release of TXB2 and FPA. The influence of antiplatelet agents on these end points will be determined.

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Christian Haudenschild, M.D., Collaborating Investigator
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Ralph C. Ito, Ph.D., Collaborating Investigator

DEPARTMENT OF MEDICINAL CHEMISTRY AND DEPARTMENT OF MEDICINE,
UNIVERSITY OF TENNESSEE CENTER FOR THE HEALTH SCIENCES,
MEMPHIS, TENNESSEE
Surface-Active Antithrombotic Agents for Prostheses
GRANT NUMBER: 5 R01 HL 22236-06

The work on novel platelet aggregation inhibitors continues to be rewarding. U.S. Patent 4,443,450 was issued April 17, 1984. Two other American patents are pending; also pending are 11 foreign patents on five continents. The basic premises of our findings are summarized in Blood Platelet Function and Medicinal Chemistry (Lasslo, ed), New York: Elsevier, 1984: 252-63/270-3; cf. Lasslo, Fed Proc 1984;43:1382-89; Lasslo and Dugdale, Proc Cardiovasc System Dynam Soc, in press.

More recently, additional observations have been reported on the effect of our compounds on human blood platelet function, Lasslo et al., Biochim Biophys Acta 1984;772:84-92, and their impact on polymer-induced platelet clustering and retention was examined, Lasslo et al., Med Prog Technol, 1984;10:71-88.

The effect of one of our most potent compounds on human blood platelet structural physiology further substantiated our interpretation of the mechanism by means of which our carbamoylpiperidine derivatives exert their action. This congener exerts, indeed, stabilizing action on platelets at the level of the dense tubular system in surface membrane complexes known to sequester platelet calcium. It appears to reinforce membrane surfaces interacting with the external environment, rather than by acting on critical sites in the interior of the cell (Lasslo and White, Biochim Biophys Acta, in press).

Andrew Lasslo, Ph.D., Principal Investigator
Marion Dugdale, M.D., Coprincipal Investigator

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BAYLOR COLLEGE OF MEDICINE
Response of Cultured Endothelial Cells to Flow
GRANT NUMBER: 2 R01 HL 23016-06

The qualitative and quantitative nature of the physical forces accompanying blood flow that vascular endothelial cells can withstand is not known. However, it has become increasingly evident that hemodynamic shear stresses have an important role in both the normal physiology and the pathobiology of vascular endothelium.

To simulate the hemodynamic environment of the circulation and examine the effect of various fluid shear stresses on the endothelium, we have developed a constant head flow apparatus to subject cultured cells to steady as well as pulsatile shear stress. Human umbilical vein endothelial cells varied their prostacyclin production, microtubule structure, cell shape, and cell orientation with time under shear stress.

Prostacyclin production increased sharply with the onset of steady flow (10 dyn/cm^2), then decreased to an average of 61 + 8 pg/10^6 cells/min. Endothelial cells subjected to pulsatile flow (8 to 12 dyn/cm^2, 1 Hz) showed a similar initial peak in prostacyclin production but leveled off to a steady state production rate (at 6 hours) that averaged 2.2-fold higher (136 $\pm$ 70 pg/10^6 cells/min) than cells subjected to steady flow.

Compared to bovine aortic endothelial cells, human umbilical vein endothelial cells resist alignment under 50 dyn/cm^2.

Cells in only 4 of 15 experiments aligned parallel to the direction of flow within 48 hours, whereas alignment required 24 hours in most experiments on bovine cells.

Labeling of the cells with fluorescently tagged antitublin revealed a full cytoplasmic microtubule complex in the cells subjected to shear stress. The microtubules in the aligned cells were always parallel to the long axis of the cell, whether the cell's long axis was parallel to the flow direction.

To simulate the influence of pressure on the vascular endothelial and smooth muscle cells, we have designed an apparatus that uniaxially stretches the cells after growing them on a compliant substrate (Mitrathane, Mitral Medical International). Both smooth muscle cells and endothelial cells align perpendicular to the axis of stretch (10 percent strain, 1 Hz, 3 days).

These studies suggested that shear stress and strain play significant roles in endothelial and smooth muscle cell structure and function.

Suzanne G. Eskin, Ph.D., Principal Investigator
Christopher L. Ives, Ph.D., Research Associate
Larry V. McIntire, Ph.D., Collaborating Investigator
Charles L. Seidel, Ph.D., Collaborating Investigator

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BATTELLE COLUMBUS LABORATORIES
A Molecular Level Approach to Blood Materials Interaction
GRANT NUMBER: 5 R01 HL 24015-06

Past work has shown that spectra of adsorbing proteins from protein solutions (including blood) can be obtained in virtually real time by the use of attenuated total reflection, Fourier transform infrared spectroscopy. A dual channel cell has been designed that is suitable for flow studies at linear rates approximating those in a medium-sized artery. The cell can be used in a chronic shunt with an awake, intact, nonanticoagulated animal. Recent and planned emphasis has been on (a) the more detailed interpretation of the complex spectra; (b) compensation for the spectral contribution of the bulk, nonadsorbed proteins, which in the case of blood exceeds that of the adsorbate; and (c) the identification and the effect on the protein adsorption of low-molecular weight species in blood that diffuse to the surface before the proteins. This last effort arises from earlier observations that in the first minute of exposure of a surface to blood, infrared adsorption bands not corresponding to any major proteins have been seen before albumin of other plasma proteins appear. These bands have been shown to arise from species with molecular weight less than approximately 1,000 daltons, which is in accord with the faster diffusion rate, enabling them to be seen before the proteins. There are indications that one or more of these small compounds, through their earlier arrival and adsorption, modify the adsorption of the proteins and thus can be of importance in blood-material interaction. Efforts are under way to identify these compounds and determine their influence on the adsorption of blood proteins on foreign surfaces.

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David J. Fink, Ph.D., Coinvestigator
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Timothy B. Hutson, Coinvestigator
Robert J. Jakobsen, Coinvestigator

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DIVISION OF LABORATORIES AND RESEARCH, NEW YORK STATE DEPARTMENT OF HEALTH
Blood-Materials Interactions: The Bridge Problems
Grant NUMBER: 5 R01 HL 24017-06

A wide variety of physical and chemical agents have been screened for effects on platelet retention from native whole blood and on platelet adhesion from citrated whole blood flowing through conventional glass bead columns. Spontaneous and chemically induced detachment of platelets from these columns into flowing or gently mixed anticoagulated blood, hard-spun plasma, or saline have also been studied. Paradoxically, agents which induce platelet aggregation in platelet-rich plasma (PRP) inhibited retention (platelet/plasma multilayer formation) and also depressed the rate of the primary phase of adhesion (monolayer formation). The phenomenon seemed equivalent to the transient refractory state of stimulated platelets when collisions are minimized, as occurs in unstirred or diluted PRP. Glucosamine and colchicine, which are known to inhibit fibrogen binding by stimulated platelets, completely abolished the primary phase of adhesion. In addition, agents that directly affect ethylenediaminotetraacetate or compete (glucosamine) for the fibrinogen receptor or cleave (Ancrod) fibrinogen promoted detachment.

The results further support the concept that fibrinogen "bridges" to the substrate and between platelets are important to both adhesion and retnetion in glass bead columns.

W. Jean Dodds, D.V.M., Principal Investigator
John A. Bergeron, Ph.D., Coinvestigator

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UNIVERSITY OF TORONTO
Fate of Surface-Bound Heparin
GRANT NUMBER: 5 R01 HL 24020-06

This research has focused on the interactions of surface-bound heparin with blood, with particular emphasis on testing the validity of the concerns of critics regarding the use of heparinized materials in long-term applications: (1) a heparin microenvironment is necessary; (2) saturation of the heparin occurs; (3) there is enhanced consumption of clotting factors; and (4) platelet activation is augmented.

For research, heparin is immobilized onto polyvinyl alcohol (PVA) via its terminal serine. The heparin is released too slowly ($\sim 10^{-4}$ g/cm^2·min) to create a microenvironment at the blood interface so that the observed in vitro (partial thromoplastin time, thrombin time, chromogenic substrate) and ex vivo (parallel flow atrioventricular shunt) thromboresistance must be attributed to the ability of the bound heparin to potentiate the antithrombin III (ATIII) inactivation of thrombin. The surface-bound heparin on a heparin-PVAcoated polyethylene (PE) tube is able to retain its biological activity. The bound heparin appears to act catalytically and is not consumed by prior exposure to thrombin and ATIII. ^{125}I-thrombin-ATIII complexes, formed on heparin-PVA beads, were displaced from the beads by defibrinated plasma but not by phosphate-buffered saline (PBS) (pH 7-4, PBS).

There was little significant difference in the number of platelets adhering to heparin-PVA and PVA gels without heparin in a static test with washed porcine platelets, in the Feuerstein flow system with washed human platelets, in the degree of release by the washed human adherent platelets, or in bead column retention with citrated canine whole blood. Therefore, we hypothesize that surface-bound heparin per se has little impact on platelet activation. Rather, it appears that the underlying surface (here PVA) dominates the interaction of the material with platelets and that its platelet reactivity determines the extent of release and aggregation.

To improve the (short-term) platelet compatibility of PVA and heparin-PVA, prostacyclin or PGE_1 is to be immobilized, the former using a method similar to Ebert et al. (J Biomed Mater Res 1982;16:629).

We continue to focus on the behavior of platelets in contact with heparinized tubing, since this is the critical concern regarding its use in the cardiocirculatory assist devices and blood-handling procedures that await the development of blood-compatible materials.

Michael V. Sefton, Sc.D., Principal Investigator
Mark W. C. Hatton, Ph.D., Coinvestigator
Walter Zingg, M.D., Coinvestigator

CASE WESTERN RESERVE UNIVERSITY
Long-Term Biodegradation of Elastomeric Biomaterials
GRANT NUMBER: 5 RO1 HL 25239-05

The goal of this project is to determine the effect of the physiological environment on the long-term stability of polymeric biomaterials. This study examines the effect of in vitro exposure to enzymes on the performance properties of Biomer, a segmented polyurethane used in blood-contacting devices. Ultrathin films were treated for periods from 1 to 6 months at 37° C with two proteolytic enzymes. Papain is similar to cathepsin B, a thiol endopeptidase released during the inflammatory response. Urease is released by leukocytes during the inflammatory response.

A 10 to 20 percent decrease in number average and weight average molecular weights by gel permeation chromatography was measured after exposure to papain for 6 months. Detection of free amine and hydroxyl groups by attenuated total relection-fourier transform infrared spectroscopy (ATR-FTIR) indicates that chain cleavage occurs by hydrolysis of both urea and urethane linkages. No change in molecular weight was observed after 6 months' treatment with urease. Nevertheless, the appearance of free amine absorptions by ATR-FTIR is strong evidence that surface degradation has occurred. Since the molecular weight of urease is 473,000 compared to 20,700 for papain, urease action appears to be confined to the surface; whereas, the bulk of the polymer film is accessible to papain.

The treatment had no significant effect on the modulus, the ultimate tensile strength, or the fracture strain. This is not surprising since above 40,000, the critical value, these properties are not sensitive to molecular weight. Nevertheless, exposure for longer peiods of time could result in deterioration of the tensile properties. Undesirable consequences were observed in mechanical tests that measured cumulative damage effects. The high-strain-fatigue lifetime was shortened considerably by treatment with either urease or papain. This effect is attributed to premature initiation of macroscopic cracks at surface defects caused by degradation.

Efforts to examine the cellular biocompatibility of various biomedical polymers continue. The biocompatibility of low-density polyethylene and a cytotoxic polyvinyl chloride has been investigated using the in vivo cage implant system. The cytotoxic polyvinyl chloride stimulated an intense acute-phase inflammatory response and, at later times, an intense and increasingly chronic inflammatory response. This system is being used to investigate the stability of Biomer and other candidate

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blood-contacting polymers under accelerated inflammatory conditions. Cellular biocompatibility studies of the NHLBI reference materials are currently under investigation.

P. Anne Hiltner, Ph.D., Principal Investigator
James M. Anderson, M.D., Ph.D., Coinvestigator

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UNIVERSITY OF WASHINGTON
Surface and Bulk Structure of Polyetherurethanes
GRANT NUMBER: 2 RO1 HL 25951-04

The central hypothesis of this program is that the surface structure of polyetherurethane (PEU) polymers is an important and systematic determinant of the blood compatibility of this class of polymers. Since the surface structure and the bulk structure of PEU's are usually different, if we can understand the factors that influence the surface structure, we can rationally design more blood-compatible PEU's. Major projects have been initiated in the areas of synthesis, surface characterization, and biological reaction to PEU's. Synthetic projects involve the synthesis of two classes of PEU materials with alternate soft-segment blocks, PEU-polydimethyl siloxane and PEU-polyalkyl methacrylate, and one PEU with a fluorinated hard segment. These will be studied for molecular weight distribution and surface segregation. Also, new polyurethane surfaces have been prepared via the addition of low-molecular-weight materials into polyurethane casting solutions. The surface properties of these blends are investigated by electron spectroscopy for chemical analysis and peel-strength measurements. Finally, the biological properties of the PEU's synthesized under this program are being studied via protein adsorption measurements, laser-light-scattering emboli detecting, and in vitro cell-culture experiments. The cell-culture measurements suggest that PEU's can be synthesized that induce the lysis of cell membranes. The significance of this observation is under investigation.

Buddy D. Ratner, Ph.D., Principal Investigator
Amarjeev Kaul, Ph.D., Investigator

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STANFORD UNIVERSITY
PAA Adsorption on Polymers Using TIRF and FTIR/ATR
GRANT NUMBER: 2 R01 HL 27187-04

The interactions of proteins with solid surfaces are complex and not well characterized. Factors requiring study include adsorption and desorption kinetics, equilibrium between surface and solution proteins, and conformational aspects of the adsorbed protein layer.

Total internal reflection fluorescence (TIRF) is a technique especially well suited to the in situ study of protein/surface interactions. In TIRF, an evanescent wave, generated at the point of total internal reflection of a laser beam directed at an interface between two transparent media with differing indices of refraction, is used to excite fluorescent molecules close to or adsorbed to the interface.

Our work began with the development of a TIRF apparatus, which was used in preliminary studies of the adsorption of bovine serum albumin (BSA), fibrinogen, and γ-globulin onto silicone rubber. This work was continued with the construction of a second general TIRF apparatus. The adsorption of BSA and fibrinogen onto cross-linked polydimethyl siloxane (PDMS) from flowing solutions was examined. These studies established TIRF as a useful tool in the investigation of protein adsorption phenomena. The application of TIRF to the study of competitive adsorption was also demonstrated with studies of adsorption from BSA/fibrinogen mixtures.

The relationship between surface properties and the kinetics of adsorption was then investigated. The adsorption of BSA onto six surfaces exhibiting a wide range of surface functionalities was studied. The results were compared to a mathematical model describing the hydrodynamic environment at the adsorbing surface to quantitatively determine the effects of mass transport limitations on the adsorption process. It was found that the observation of intrinsic protein adsorption kinetics is often confounded by mass transport limitations.

Our current efforts focus on the study of the conformation of adsorbed proteins and its effect on the adsorption process. Preliminary fluorescence polarization studies on an adsorbed BSA layer suggest that, as the bulk solution pH increases above the isoelectric point of BSA, the adsorbed layer expands due to increasing electrostatic repulsion of the BSA molecules. Further studies concerning the conformational nature of adsorbing proteins include investigations of the interactions of antibodies with adsorbed protein and the study of adsorption of small, disulfide-rich proteins whose conformations have been altered by disulfide bond reduction.

Channing R. Robertson, Ph.D., Principal Investigator

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CASE WESTERN RESERVE UNIVERSITY
Human Vascular Grafts: The Blood/Materials Interaction
GRANT NUMBER: 5 R01 HL 27277-04

This project is directed toward obtaining a better understanding of the blood/materials interaction in human synthetic vascular grafts. The studies involve human blood interactions with vascular graft materials and the compositional analysis of the pseudointima that develops on human vascular grafts.

To date, we have completed an extensive biochemical and histological analysis of Dacron vascular prostheses recovered from human recipients. Additional studies on pseudointima/neointima on vascular prostheses from canines are being carried out to provide information on species differences. These studies form the basis for an understanding of those factors that influence pseudointima/neointima development. In recovered human vascular prostheses, we have found that in successful Dacron grafts, patent at the time of removal, the collagen content of the pseudointima was low (< 5 percent) but contained an unexpectedly high proportion of type V collagen relative to types I and III. In human grafts stenotic or occluded by fibrous tissue at the time of removal, the fibrous tissue filling the lumen contained primarily type I collagen. In most Dacron grafts, the collagen in the tissue occupying the fabric interstices was rich in type III, relative to the pseudointima or the outer capsule.

A recirculating, in vitro system has been used to study the interaction of human blood with vascular graft materials. Blood samples, taken prior to and during the recirculation, were assayed for platelet count, platelet retention ability, platelet factor 3, platelet release (platelet factor 4 and β-thromboglobulin levels), platelet aggregation, leukocyte count, complement activation (C5a), prothrombin time, partial thromboplastin time, fibrinogen level, and fibrinopeptide A(FpA) level. Both heparin and citrate have been used as anticoagulants. In a study comparing 8 mm ID silicone, e-polytetrafluoroethylene (e-PTFE), and crimped knitted Dacron, Dacron was more platelet and coagulation activating than either e-PTFE or silicone, the latter two being similar. This was shown for Dacron relative to silicone by a decrease in platelet count, an increase in plasma PF4 and βTG levels, an increase in platelet factor 3 availability, and an increase in FpA levels. With heparin, Dacron showed complement activation concomitant with a decrease in neutrophil count, possibly signaling neutrophil adhesion. The effect of preclotting Dacron on platelet function also has been studied.

This in vitro perfusion system has been adapted to study small diameter (4 mm ID) vascular grafts at low flow rates. When e-PTFE was compared with silicone, platelet counts for both materials remained near baseline at 100 and 75 ml/min. However, when the flow rate was lowered to 50 ml/min, the platelet count dropped to 70 percent of baseline for the

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silicone with that for e-PTFE remaining stable. Preliminary studies with 4 mm ID NHLBI-standard reference materials at flow rates of 50, 75, and 100 ml/min show little difference in platelet activation when compared with the silicone rubber used in these experiments.

James M. Anderson, M.D., Ph.D., Principal Investigator

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UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT DALLAS
Blood Trauma from Microporous Membrane Oxygenators
GRANT NUMBER: 5 R01 HL 28690-04

Our research has focused on developing visualization methods to aid in understanding the early events in protein adsorption on blood-contacting materials. We have also devoted considerable effort to developing a novel method for favorably altering the blood compatibility of polymers, treating surfaces to allow preferential binding of endogenous serum albumin.

Visualization of protein adsorption in prior years' work by partial gold decoration and immunoferritin triethylenemelamine (for a number of polymers and pyrolytic carbon) has been substantiated this year by conventional radiolabel-based surface concentration measurements. Fibrinogen, and especially albumin films, are more extensive, closely packed, perhaps thicker, and bound more tenaciously on pyrolytic carbon surfaces than on typical hydrophobic polymers. The organization of adsorbed protein on hydrophobic polymers is quite different: fibrinogen creates a reticulated network and albumin-sparse microaggregation.

Using commercially feasible surface alkyl and acylation techniques, Cuprophan and other cellulose derivatives, Dacron polyester, and a number of polyurethane formulations have shown marked increases in albumin affinity compared to underivatized controls. Albumin coats rapidly and densely on the derivatized polymers, compared to slow and sparse microaggregate coatings on controls.

A total internal reflection fluorescence (TIRF) technique has been perfected, utilizing a pulse nitrogen laser system, allowing us to probe the conformation of bound albumin. Albumin binding experiments (from solution to a quartz substrate) have been completed and have produced interesting results. Comparison of fluorescence lifetime in bulk solution and in the surface-adsorbed state indicates a statistically significant decrease in quantum yield upon surface adsorption. Quantum yield of albumin in the adsorbed state is similar to that observed in bulk solution at pH 3.8, close to the isoelectric point. Similar quantum yield for bulk albumin solution is observed with heat denaturation of the protein. Similar results were obtained for purified albumin monomer and unpurified fraction V. Photobleaching and other artifacts that have hampered previous research in this area have been satisfactorily resolved with this instrumentation system. Results suggest that significant alteration of structure (unfolding) accompanies adsorption of albumin on quartz and suggests an interesting series of experiments.

We continue to obtain promising results for small vessel vascular prostheses treated to adsorb and retain serum albumin from blood. Our results provide no conflict with the hypothesis that the hydrophobic interaction between albumin and C_{16} and C_{18} alkylated polymers allows

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maintenance of a thromboresistive coating of serum albumin for an extended period of blood exposure.

Robert C. Eberhart, Ph.D., Principal Investigator
Frederick Grinnell, Ph.D., Coinvestigator
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BAYLOR COLLEGE OF MEDICINE
Effects of Shear Stress on Red Blood Cells
GRANT NUMBER: 5 R23 HL 30834-02

Red blood cells (RBC) are subjected to shearing forces as a result of circulation through artificial devices such as cardiopulmonary bypass pumps, renal dialysis units, or circulation through prosthetic heart valves. Red blood cells in the normal circulation probably experience a low level of shear stress that may increase during rigorous exercise. Shear stresses above 1,500 dyn/cm^2 have been shown previously to cause fragmentation and hemolysis, while subhemolytic shear stresses have been shown to produce a damaged cell marked by decreased deformability and increased calcium content.

We have investigated further the relationship between subhemolytic shear stress, calcium uptake, and the observed decreased red blood cell deformability. Red blood cells were sheared in a concentric cylinder viscometer at stresses between 500 and 1,500 dyn/cm^2. Deformability was assessed by a Nuclepore filtration technique. It was found that varying the external calcium concentration had no effect on the change in RBC deformability as measured by Nuclepore filtration. RBC's suspended in 2.0 mm calcium were subjected to shear stress in the presence of Calcium-45 radioactive label. These cells showed a shear stress-related uptake of the labeled calcium and also extrusion of the calcium in postshear incubation studies. Furthermore, the presence of equimolar amounts of EGTA, a relatively specific calcium chelator, completely blocked subhemolytic shear-induced calcium uptake. RBC's sheared in the presence of calcium and EGTA had the same decrement in deformability that occurred in cells sheared in the presence of calcium without the chelator. This finding suggests calcium uptake resulting from shear stress does not substantially contribute to the decreased deformability of the subhemolytically sheared RBC's.

In addition, we found that the conditions of shear greatly influenced calcium uptake. If cells are sheared in a higher viscosity medium such as dextran, there are greater degrees of calcium uptake by cells, hemolysis, and potassium loss than those seen for the same shear stress achieved at higher shear rates when the suspending medium is closer to a physiologic viscosity.

From our studies, we conclude that calcium uptake after low levels of sheer stress appears to be relatively unimportant because most of it is immediately extruded from the cell. The increased calcium leak is probably secondary to more fundamental alterations in the red cell membrane. The importance of calcium uptake in cells subjected to hemolytic shear stresses or when physiologically impaired red cells of uremic individuals or of sickle cell disease patients are sheared remains to be seen.

Mark M. Udden, M.D., Principal Investigator

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UNIVERSITY OF WASHINGTON
Mechanisms of Arterial Graft Failure
GRANT NUMBER: 5 RO1 HL 30946-02

Failure of long-term synthetic arterial bypass grafts has been attributed in part to anastomotic stenosis, but the pathological basis for this has not been determined. Which cells participate in the formation of the stenosis and the relationship between normal healing and the pathological development of anastomotic narrowing have not been delineated. This study examined early wound healing in 4 mm polytetrafluoroethylene (PTFE) arterial bypass grafts placed in babcons. In this primate model, endothelium and smooth muscle cells (SMC) derived from the cut ends of adjacent artery form the new intima and migrate together along the luminal surface of the graft at approximately 0.2 mm/day. Both cell types proliferate in association with the growing edge. In addition, both endothelium and SMC located discretely over anastomoses continue to proliferate despite complete endothelial coverage. The intimal cross-sectional area in this region is always greater than that over adjacent graft. Fibroblasts are invariably found in the graft matrix and adventitia and do not contribute to formation of intima. We hypothesize that anastomotic narrowing might be due to chronic endothelial injury and turnover associated with continued SMC proliferation and intimal thickening.

Alexander W. Clowes, M.D., Principal Investigator
Allen M. Gown, M.D., Collaborating Investigator
Stephen R. Hanson, Ph.D., Collaborating Investigator
Michael A. Reidy, Ph.D., Collaborating Investigator

BIOMETRIC SYSTEMS, INC.
Anatomical Substitutes With Proclivity for Cell Lining
GRANT NUMBER: 1 R43 HL 32382-01

Biomaterials are needed for a wide variety of functions and environments within the body, requiring a wide variety of physical properties for their construction and stable functioning. A major difficulty is found in acquiring a biocompatible surface in combination with the required physical properties (e.g., strength, elasticity, permeability and flexibility) stable over a long period of use in the body. A major advance in biomaterials technology would result from the ability to readily tailor the surface of preformed physically optimized implant devices to provide the proclivity for rapid overgrowth of a stable natural cell surface lining.

Fibronectin (FN) and laminin (LM) are important polypeptide attachment factors for mammalian cells in culture. These proteins are potent stimulators of cell migration in vitro. FN, LM, and combinations of these proteins are coupled to the surface of prostheses plastics using heterofunctional cross-linking photoreactive reagents. Plastics studied in this project include polyvinyl chloride, polypropylene, polyethylene, polystyrene, polyurethane and polytetrafluoroethylene (disks and tubing).

Preliminary studies using bovine endothelial cells suggest that these factors stimulate cell migration and overgrowth of the surface of artificial vascular plastics. Human endothelial cells will be used in future tests to document regrowth over factor-bound matrix on similar plastics. The canine model will be used for in vivo bilateral femoral graft studies.

If a nonthrombogenic human endothelial cell lining were possible, the impact upon modern surgical practice would be significant. A nonthrombogenic implantable device would clearly increase the market.

Peter H. Duquette, Ph.D., Principal Investigator
Ruth B. Johnson, M.S., Collaborating Investigator
Peter Nash, Ph.D., Collaborating Investigator

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Primary Reference Materials

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MERCOR, INC.,
A THORATEC COMPANY
Procurement of Primary Reference Materials
CONTRACT NO: N01-HV-92933

The objectives of this contract are the fabrication, characterization, and distribution of large quantities of silica-free polydimethyl siloxane (PSX) for use as primary reference materials (PRM's) by NHLBI-designated laboratories to facilitate comparison of test systems and biomaterials data.

In fabricating both the sheet and tubing configurations, silica-free room temperature vulcanizing (RTV) PSX fluid was synthesized and applied to a substrate material under class 100 cleanroom conditions. Sterilized samples from each fabrication lot were subjected to characterization by three bulk and four surface techniques: differential scanning calorimetry, thermogravimetric analysis, swelling/extractables, scanning electron microscopy, electron spectroscopy for chemical analysis (ESCA), γc, and attenuated total reflection infrared spectroscopy. A master file is kept, which documents these results as well as the process conditions and characterization for each step from the synthesis of the RTV through the sterilization of the packaged samples.

Samples from sheet lots 03 and 04 and tubing lots 01 and 02 have been subjected to quality assurance testing to confirm the stability of the PRM. The testing techniques employed are equilibrium swelling/extractables, γc, and ESCA. To date, all of the lots of sheet and tubing PRM have remained stable during storage.

ESCA analysis performed on each lot by the University of Utah confirms the chemical purity of the RTV-coated surface. Typical ESCA results give the C:O:Si ratio of 2:1:1 as expected for pure PSX.

Upon notification from NHLBI, samples are distributed to the investigators. Included with each shipment is a package insert containing a brief description of the material, handling and storage conditions, characterization report forms, current quality-assurance test results, and a brief description of the characterization methods used.

To date, PSX PRM's have been distributed to 15 investigators in five countries.

At the completion of this contract (September 31, 1984), Mercor, Inc., will continue to distribute the remaining 23,000 PSX primary reference materials.

Robert S. Ward, Principal Investigator
Kathleen A. White, Analytical Chemist

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Mechanical Circulatory Support: Energy Transmission

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THERMEDICS, INC. (NEW ENGLAND MEDICAL CENTER)
Research and Development of Systems for Transmitting Energy Through Intact Skin
CONTRACT NUMBER: NO1-HV-02903

A transcutaneous energy transmission (TET) system has been developed to deliver electric power to permanent implanted ventricular assist systems (VAS's) and total artificial hearts (TAH's) without passing conductors through the skin. The TET system inductively couples energy between a superficial coil of wire resting on the skin surface and a coil implanted 1.5 cm deep. Together, the coils form a "transcutaneous transformer." The system offers an alternative to percutaneous power leads, effectively buying a solution to the problem of infection at the site of a large-diameter, percutaneous-access device with increased electrical complexity and decreased energy transfer efficiency.

The transcutaneous transformer is a loosely coupled air core transformer. The implanted (secondary) coil contains 16 turns of wire arranged to fit within a desired geometry. The geometry was chosen to produce a shallow mound when the coil is implanted subdermally at a depth of approximately 1.5 cm. The superficial (primary) coil contains three turns of wire wound in a flat spiral. The inner diameter of the superficial coil was chosen to approximate the perimeter of the mound created by the implanted coil. These mating shapes resist misalignment of the coils, which will degrade transformer performance. In humans, an elastic bandage should suffice to hold the lightweight primary coil in place. Proper alignment is readily achieved by nontechnical persons.

The implanted coil is a composite structure of carefully chosen materials. The coil is wound from copper Litz wire (3/5/20/38), whose characteristics were selected to minimize coil heating due to I^2R losses. The copper conductors in the wire are protected from degradation by body fluids by a barrier of specially formulated butyl rubber, which is highly impermeable to moisture. The butyl-coated coil is encapsulated in a polyether-based elastomeric urethane such that surrounding tissues are presented with an abrasion-resistant, nontoxic surface of demonstrated tissue compatibility.

A series of studies were undertaken to: (1) evaluate the biocompatibility of the materials, (2) study the tissue response to the thermal and radiofrequency characteristics of these systems, (3) determine whether the size and shape of these devices were suitable, (4) study the ability of the skin overlying the implanted coil to regenerate if traumatized, and (5) determine the extent to which system migration occurred following implantation. While it was not possible to study each of these considerations in detail, our findings, based on tests of 18 systems implanted in nine Pitmann-Moore miniature pigs, may be summarized as follows: Essentially no differences were detected in the tissue response between unpowered and actively powered TET systems in experiments ranging up to 22.5 months. The tissue response was typical

of a mild, chronic, foreign-body reaction to any nonbiologic, implanted object. The implanted secondary coil was "walled off" with a dense collagenous capsule, which was generally quite fibrous and only moderately vascularized. The surrounding tissue remained well vascularized and exhibited normal tissue structure, tone, and vitality. The implant site appeared adequately perfused and was observed to regenerate without incidence when injured by animal trauma. The skin surface was characterized by a normal appearing epidermis, unaffected by the presence of the primary coil, and was covered by a normal complement of hair. No evidence of system sinking or migration was detected up to the 22.5-month period. However, the mound of skin overlying the secondary coil characteristically lost some of its prominence in cases where the animal's weight increased dramatically.

Based on these experiences, the series II TET system appears to be well accommodated by the host. The materials, size, shape, thermal, and radiofrequency characteristics of these systems appear satisfactory for long-term transmission of energy.

Craig Sherman, Principal Investigator
Ben Daly, Coprincipal Investigator

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NOVACOR MEDICAL CORPORATION
(DEPARTMENT OF SURGERY, SCHOOL OF MEDICINE, STATE UNIVERSITY OF NEW YORK AT STONY BROOK)
Electrical Energy Transmission Technique Development
CONTRACT NUMBER: N01-HV-72933

The "belt" skin transformer (BST) consists of a pair of narrow, flexible, concentric coils (located around the waist). It exhibits an inherently high and stable coupling efficiency and represents an attractive alternative to percutaneous leads for powering permanent implanted cardiac prostheses.

Long-term tissue compatibility, electromagnetic efficacy, mechanical longevity, and superior compliance are critical design factors. An integrated secondary and connector development effort led to the final, single-turn, flat, helical configuration. The 10 conductors are electrically parallel, nearly eliminating potential gradients between them or to the surrounding tissue. A small, toroidal step-up transformer matches this low voltage to the VAS load.

Secondary belts of varying geometry, elastomeric materials, and connector design have been implanted in a total of 63 dogs. Early experiments were designed primarily to evaluate alternative elastomers. Chemical and mechanical tests of explanted belts, fabricated from several compatible materials, led to selection of Sil-Med SM4050 heat-vulcanizing silicone rubber for the secondary encapsulant. Its superiority was borne out by continued excellent secondary performance in vivo for periods exceeding the 2-year design goal.

Long-term in vivo evaluation of complete functional BST's was conducted in eight animals. An implanted capacitive load permitted chronic secondary excitation at full BST operating power but without significant intracorporeal heat dissipation. Primary belts having conductors woven into a porous, soft elastic band proved easier to maintain for long periods on dogs and, therefore, supplanted the earlier molded-elastomer primaries. Continuous electrical excitation and BST performance data management were provided by a microprocessor-controlled central power and data acquisition system.

Only one of the eight long-term secondaries, fabricated from Dow-Corning MDX 4-4210 (the alternative material), failed in vivo. In most cases, Sil-Med belts showed little degradation over the test period. In two cases, localized conductor corrosion occurred in the vicinity of small tears or nicks in the elastomer, which may have occurred at implant and did not propagate.

Six of the eight long-term secondaries remained implanted for at least 1 year. Infection prompted the termination of one experiment, while a second animal was lost to unrelated causes. Excluding these two, the long-term functional BST evaluations averaged more than 20 months, with

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the longest exceeding 29 months. Explanted belts were typically in excellent condition and enclosed in a thin, compliant tissue capsule. This experience strongly supports the viability of the belt skin transformer as a suitable power source for long-term circulatory assist devices.

Peer M. Portner, Ph.D., Principal Investigator
Sylvain Pitzele, M.D., Ph.D., Principal Investigator/Subcontractor
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SINAI HOSPITAL OF DETROIT
(UNIVERSITY OF MICHIGAN)
Development of a Percutaneous Energy Transmission System
CONTRACT NUMBER: NO1-HV-82921

To develop a percutaneous access device (PAD) free of infection, through which pneumatic, hydraulic, or electrical energy may be transmitted for long periods of time, our group investigated a technique whereby a biological seal between the PAD and the surrounding tissue was established through autologous fibroblasts grown on the transcutaneous portion of the PAD neck. We observed that the fibroblasts form confluent multilayers and extend cell processes into the nanopores in the PAD neck in vitro. Upon implantation of the PAD with such an autologous, living, coated, nanoporous (ALCON) surface, epithelial migration was usually (in 8 out of 11 cases) inhibited for an extended period of time as reported earlier.

At last year's contractors' meeting, we reported a modification in the PAD implantation technique, from a single-stage to a multistage procedure, which was designed to improve the consistency of results. Long-term evaluation of PAD's using both techniques are proceeding.

Six PAD's (including two controls) were implanted using the single-stage procedure, and 12 PAD's (including two controls) were implanted using the multistage technique. One of the control PAD's was removed following infection, and the remaining three show variable degrees of skin retraction, an early sign of failure, around the implant. In the experimental group, two multistage implants had to be removed prematurely, at 4 and 3-1/2 months, respectively, due to trauma of unknown origin in one and erosion of the PAD flange in the other. Histological sections from both groups clearly demonstrated inhibition of epithelial downgrowth, a result consistent with our previous findings.

The remaining 12 implants appear clinically satisfactory for periods up to 15 months postimplantation to this date. No differences in the results from the two implantation techniques are so far apparent. All implants are scheduled for removal at 24 months postimplantation.

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ST. ELIZABETH'S HOSPITAL--TUFTS UNIVERSITY
(THERMEDICS, INC.)
Development of Percutaneous Energy Transmission Systems
CONTRACT NUMBER: NO1-HV-82919

Percutaneous energy transmission system (PETS) development has continued in our laboratories for over 6 years. Our initial prototype system consisted of five components and our biomaterials. The carbon-coated titanium button was designed to minimize reaction at the epidermis. The porous polytetrafluoroethylene (PTFE) was designed to encourage infiltration of connective tissue within its pores and the development of a collagen-biomaterial seal to inhibit epidermal migration and sinus formation. The Dacron velour was designed to promote rapid tenacious bonding in deep tissues. The subcutaneous skirt was to provide strain relief to the system as a whole and to prevent distraction of the epidermis away from the relatively weak tissue-PTFE bond. With the exception of eliminating the conduit for testing purposes, very few changes in overall design have been made over the years, and our in vivo experience with these systems now consists of 98 implantations in 49 miniature pigs.

Changes in design have included: (1) elimination of the flange, which trapped keratinous debris at the margin of the system and promoted wide sinus formation, (2) elimination of the deeper conduit to facilitate fabrication and implantation because this portion of the device was not part of our primary evaluation objective, and (3) limitation of the PTFE to the horizontal and only a small portion of the vertical part of the PETS terminal because the sinus invariably reaches the radius and horizontal portions of the system and because forming the PTFE on the more vertical portion of the system produces pore distortion during fabrication. Extensive evaluation of available porous materials in vivo encouraged us to continue utilizing PTFE and Dacron velour. However, these experiments suggested that PTFE in a 15:1 expansion ratio (Impra, Inc.) would provide better tissue penetration and adhesion than the standard PTFE in a 5:1 expansion ratio (Gortex) and that carbon impregnated PTFE in a 15:1 expansion ratio (Impra) would be superior to PTFE without carbon. Furthermore, evaluation of various methods of rewetting the PTFE at the time of implantation demonstrated that saline introduced under vacuum was as effective as other methods and did indeed improve tissue adhesion to PTFE. Scanning electron microscopy studies demonstrated that forming the PTFE in a flared configuration produced less pore distortion. Evaluation of various materials for the skirt demonstrated the superiority of Dacron velour in achieving exceptional tissue bonding and the ability to lessen the extensive chronic granulomatous reaction to Dacron by chemical stripping.

Histopathologic evaluation of all electively removed systems has demonstrated that by 6 months the sinus reaches the Dacron velour. However, the delay in sinus progression caused by the PTFE-tissue seal, which is broken down either biochemically or mechanically over time, allows the

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connective tissue at the Dacron to mature. At 6 months, the connective tissue appears indistinguishable from dermis and the inflammatory reaction about the Dacron has subsided. We believe this "neodermis" provides the same inhibition to epidermal migration as normal dermis.

Changes in protocol that have improved our animal models and management, have included: (1) using only miniature pigs that weigh more than 40 kg to ensure adequate growth and development; (2) including a minimal tetracycline dose in the feed as prophylaxis against group C/E hemolytic-streptococcus, which have extreme wound virulence in pigs; (3) implanting the skirt immediately under the dermis, utilizing ipsilateral implantation, which gives the animal a pain-free side in the early postoperative period and appears to minimize early trauma to the PETS implantation; (4) utilizing a dorsal implantation site, which has provided us with better PETS implant longevity, which is statistically significant when compared with other sites, and (5) bacteriologic monitoring with swab cultures and antibiotic treatment based on sensitivities when two consecutive cultures are positive (> 10^3 col/swab).

Table 1 shows our data with the PETS 2A system implanted and monitored in standard fashion.

Table 1

Series 1A Gortex 5:1	Series 1B Impra 15:1	Series 1C Impra 15:1 with Carbon	Series 1C Tethered
1. 365 E	523 - 0	446 - 0	215 0
2. 365 E	523 - 0	446 - 0	215 0
3. 371 E	525 - 0	434 - I	201 0
4. 371 E	525 - I	434 - I	201 0
5. 345 I	244 - I	334 - I	173 0
6. 287 I	154 - I	301 - I	173 0
7.			166 0
8.			126 I
9.			49 T I
10.			49 T I

*0 = Days ongoing.
E = Elective explant.
T = Trauma.
I = Explanted because of infection as of August 20, 1984.

We believe the longevities achieved with this system in an unfriendly host are significant. In every instance, the infections necessitating explant of the systems with the more expanded PTFE have occurred in association with detachment of the PTFE from the prosthesis. When the infection has been limited, it has been adjacent to an area where part of the PTFE has separated from the underlying urethane. We believe at

the present time that the PTFE-urethane bond weakens over time and that trauma initiates separation followed by infection. Further evaluation of this is under way.

We are convinced that this system will provide satisfactory performance in humans for periods of 2 years.

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Mechanical Circulatory Support

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UNIVERSITY OF WASHINGTON
(CLEVELAND CLINIC FOUNDATION)
(WHALEN BIOMEDICAL, INC.)
Development of a Thermal Ventricular Assist System (TVAS)
CONTRACT NUMBER: N01-HV-28002

The objective of this continuing program at the University of Washington Joint Center for Graduate Study (JCGS) is to develop a permanently implantable Stirling/hydraulic power source to operate ventricular assist or full-heart replacement blood pumps. Parathoracic Ventricular Assist Device (PVAD) Model 12A and 12C blood pumps are being refined under subcontract to Whalen Biomedical, Inc., with in vivo testing of System 7B and related work conducted by the Cleveland Clinic Foundation (CCF). The System 8 engine module, currently under development, is planned as the final preclinical design. Selective component fabrication of six System 8 engine modules was initiated, and fabrication of two prototype versions was completed.

In vitro and in vivo tests are currently conducted with the integrated System 7B engine module and PVAD Model 12A blood pump. Computer modeling, mockup testing, and collaboration with the subcontractors for envelope configuration and implant location contribute to System 8 development. System, subsystem, and component operation in actual or simulated duty cycles are approaches used for life testing.

A 1-month in vivo test was successfully conducted with the System 7B integrated package at CCF. The 286-lb male Holstein calf had an excellent recovery over the 30-day test period. The system demonstrated very good synchronized counterpulsation with the left ventricle. In vivo tests were also successfully conducted to evaluate the permeation characteristics of a fluid-filled compliance chamber and to study the performance of a Model 12C PVAD pump with a new 0.75 mm-thick diaphragm.

The design analysis in support of System 8 was completed. Many of the in vivo detail drawings for engine, converter, and actuator components were completed. Engine and converter major components were fabricated and functionally tested. Two prototype engine modules are undergoing shakedown testing and performance evaluation. The design of the implantable System 8 actuator/controller is nearly complete, and a prototype version has been fabricated. Cleveland Clinic has defined an engine and pump-actuator configuration for use in the human thorax that will eliminate the need for flexible hydraulic lines.

Life testing emphasizing Systems 6 and 7 critical components is continuing without failure. A complete System 7 integrated module is undergoing continuous in vitro testing. A complete System 6 engine module with a metal diaphragm has operated continuously for over 1 year. Several bellows components have now exceeded 7 years of continuous testing, representing nearly 6 billion cycles.

The current state of development provides a high level of confidence that the System 8 objectives to produce a clinically useful ventricular assist system with an 8-hour self-contained operating time for a 1-hour recharge time and a 10-year lifetime potential will be realized.

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NIMBUS, INC., AND CLEVELAND CLINIC FOUNDATION,
DEPARTMENT OF ARTIFICIAL ORGANS
Thermal Ventricular Assist System
CONTRACT NUMBER: NO1-HV-28001

This program is being conducted by Nimbus, Inc., in association with the Cleveland Clinic Foundation (CCF). The objective of this program is to develop a fully implantable, thermally powered, left ventricular assist system.

The basic system consists of a modified Stirling cycle engine, pneumatic controls and actuator, variable volume device, thermal management system, energy transmission system, and the CCF intrathoracic blood pump. Engine heat is developed by an electrically powered resistance heater. The heater is periodically energized and used to melt a volume of fluoride salt. The heat of fusion stored in the salt volume provides a thermal battery capable of powering the assist system for up to 8 hours. The periodic transfer of electrical energy across the skin is accomplished using inductive coupling. Thus, with this system, patients are supported by a totally implanted device that can be free of any external power source for a considerable period of time.

Currently two thermal systems are being built-up and checked-out for in vivo testing using CCF blood pumps. Both systems use engines that are heated continuously by electrical power. One system is a two module configuration composed of an engine connected by flexible lines to a blood pump module, which includes the pneumatic controls and actuator. The particular engine used for the two module system is a Mk 8, an earlier engine configuration. The latest engine design, the Mk 9 configuration, is used in the second thermal system. With this engine, which is considerably smaller than the Mk 8, it is possible to mount the engine with the blood pump module, resulting in a single integrated configuration.

Detailed design of a prototype thermal salt system is in progress. This system uses a Mk 9 engine contained in a salt volume section. These are integrated into one module, which is coupled by flexible lines to a blood pump-actuator controller module. In a human, such a system configuration would be accommodated by placing the blood pump module in its usual intrathoracic location and locating the engine module in the abdomen.

Supporting studies were continued on endurance testing of thermal system components. Early model engines are being run, providing data on bearing and reverser system wear. Actuator gas seals and bearings are being tested in special test fixtures, and a complete Mk 8-driven system is being run. Finally, component tests of the blood pump and variable volume device were conducted in vivo in calves.

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TEXAS HEART INSTITUTE OF ST. LUKE'S EPISCOPAL AND TEXAS CHILDREN'S HOSPITALS
(GOULD, INC. AND THERMEDICS, INC.)
Development of an Implantable, Electrically Actuated Heart Assist System
CONTRACT NUMBER: NO1-HV-02915

A permanent, implantable, electrically powered ventricular assist system (THI/Gould VAS) has been developed for ultimate clinical use in patients with end-stage cardiac failure. The system includes five major integrated components: (1) pusher-plate blood pump; (2) electrical-mechanical energy converter; (3) implantable control/power module; (4) volume compensation compliance chamber; and (5) external power supply/monitoring unit. All components of the system have been finalized and a complete operational THI/Gould VAS has been fabricated and tested. Maximum blood pump and energy converter life tests now exceed 6.6 and 3.4 years (results include: blood pump, five tests > 4 years and actuator, two tests > 2 years). The hybrid microprocessor-based control electronics have been reliable during in vivo operation and are responsive to varying physiologic demands. In vivo evaluations of thoracically implanted volume compensation compliance chambers have demonstrated satisfactory performance and minimal tissue encapsulation. In vitro tests of the internal rechargeable battery module have demonstrated discharge times and cycle life greater than 30 minutes and 2 years, respectively. Similar tests of the external battery unit yielded discharge times and cycle life greater than 10 hours and 1 year.

Study Period	Duration (Days) mean ± SD	Range (Days)
Short term (n=9) < 1 month	19±8	10-30
Intermediate term (n=14) 1-3 months	60±14	42-79
Long term (n=6)* > 3 months	135±37	95-181

*Includes studies of 181, 180, 131, 116, 108, and 95 days.

During the past year, in vivo studies included two evaluations of a redesigned short, rigid, inflow conduit with durations of 180 and 116 days. This modification, as predicted,† eliminated problems with occlusive inflow pannus formation. Maximum blood pump stroke volumes

†THI Proposal No. 29214, February 6, 1984, in response to RFP NHLBI-HV-84-1.

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of 90 ml/beat were obtained throughout both studies at rest (pump rate < 90 beats/min) and exercise (pump rate up to 120 beats/min with pump output of 10.6 l/min). Thus far, 29 chronic electrically actuated system studies have been performed in calves for durations up to 6 months with a cumulative in vivo experience of 5.0 animal years of testing (table). Taken together, these results demonstrate the potential of the THI/Gould VAS for long-term (> 2 years) mechanical circulatory support and indicate system readiness for preclinical validation.

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THERMEDICS, INC. (CHILDREN'S HOSPITAL MEDICAL CENTER)
Development of an Implantable, Integrated Electrically Powered
Left Heart Assist System
CONTRACT NUMBER: NO1-HV-02914

The program objectives are the development and evaluation of a complete, electrically driven ventricular assist system (VAS) intended for chronic cardiovascular assist, together with peripheral support and energy storage means that will permit a quasi-normal lifestyle.

The MK IV electrically powered VAS comprises a fully integrated heart assist pump, driver, controller, synchronizer, backup energy source, and power conversion unit in two implantable modules. The system can be powered from an externally worn energy source, either by a percutaneous lead or via high-frequency AC power, transmitted across the intact skin.

Central to the system is a low-speed torque motor that powers a pusher-plate assist pump at one cycle per revolution. After eject is completed, the pusher-plate is free to return toward the fill position at a rate governed solely by the rate of blood influx to the pump. This technique yields inherently high reliability because the moving parts are few (five) and operate at low speeds.

A unique feature of the MK IV system is its ability to respond instantly to changes in heart rate, which reduces the complexity of synchronous control circuitry. Weight and volume of the assist pump and driver are 0.87 kg and 405 cc. Its operating efficiency is above 30 percent.

The implantable controller subsystem contains control, synchronizer, and power conversion electronic modules, surrounded by an annular ring of 10 450 ma-hr NiCd cells. The battery provides discharge time of 40 minutes at 8 l/min and 120 mm Hg mean outlet pressure. The synchronizer and controller provide synchronous counterpulsation, if a verifiable systolic interval exists, pumping on "full" if the flow rate permits operation above a minimum beat rate, or temporary reversion to fixed rate in the presence of low flows and insufficient ventricular contractility. Weight and volume of the controller/battery unit are 0.36 kg and 160 cc.

The third implantable system element is a variable volume chamber, designed to be implanted in the pleural space. The flexible portion of the variable volume device (VVD), solution cast as a trilaminate of Biomer with a central core of butyl rubber, is adhesively bonded to a rigid titanium backing plate. It is cast in the fully distended position to allow the restorative force of the elastomer to assist pump filling. Operation of the device was verified in vivo during six active and passive animal experiments that extended for periods up to 300 days. Liquid transport across the elastomer was found to be nil; ballast

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gases that originally filled the passive chambers were replaced in a relatively short time by oxygen and nitrogen in atmospheric proportions.

In vitro testing of the completed MK IV VAS, including the variable volume device, has continued for most of this year (28×10^6 cycles) without incident or interruption. Component tests of the elastomer diaphragm have exceeded 9.5 cumulative years without failure. The longest running of these has achieved 111×10^6 cycles.

Five studies of the complete MK IV VAS were undertaken this year in calves, for a total of 174 experiment days. The longest study reached 77 days, with the final 29-day study powered by the transcutaneous energy transmission system (TETS). Counterpulsatile phasing was repeatable and responsive over the observed range of heart rates (60 to 130 beats/min) with flows observed to 7 l/min.

System characterization is now routinely performed using a direct microprocessor link between the NHLBI circulatory loop and our main computer.

We believe that the MK IV VAS has met most, if not all, of the developmental goals specified by the NHLBI guidelines. It is compatible in size and weight with humans of moderate frame size; VAD anatomic fitting studies have been performed successfully in subjects as small as 60 kg. The pumping criterion of 10 l/min at 120 mm Hg mean outlet pressure and 15 mm Hg mean inlet pressure has been achieved, and long-term evaluation of the system in vivo is in progress.

David B. Gernes, Principal Investigator
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NIMBUS, INC., AND CLEVELAND CLINIC FOUNDATION, DEPARTMENT OF ARTIFICIAL ORGANS
Development of an Electrohydraulic-Driven Left Heart Assist System
CONTRACT NUMBER: N01-HV-02911

A left heart assist system intended for patients requiring chronic cardiovascular support is being developed in this program. Relative to others, the Nimbus/Cleveland Clinic E3C system is unique in that the central anatomical location for the implanted components is the thorax; there are no components in the abdomen nor are there any diaphragmatic penetrations. Also distinctive is the electrohydraulic energy converter and the blood-contacting surface of biolized gelatin coating.

This 4-year program, now completed, has made significant progress in achieving a useful clinical device. Early effort concentrated on development of the basic blood pump-energy converter unit. Later work emphasized development of the other implanted components and refinement of the blood pump-energy converter configuration to make it accommodate a broader range of patient anatomies. In particular, during this last year, key accomplishments were made in the areas of energy transmission, variable volume management, and diagnostic monitoring.

An NHLBI-supplied transcutaneous energy transmission system (TETS) was adapted to drive the E3C energy converter, and extensive in vitro tests of TETS-driven E3C systems were conducted. Satisfactory power range and functional compatibility were demonstrated. A breadboard rectifier circuit suitable for hybridization was developed as part of this effort.

Hermetically sealed internal batteries consisting of NiCd cells contained in titanium housings were fabricated, and satisfactory capacity and performance were demonstrated in in vitro tests. Prototype wiring harnesses were fabricated using custom titanium connectors. Tests of connectors and cables submerged in 37° C saline are in progress. No trace of intrusion of water or ions is apparent after 3 months.

In vivo tests of gas-filled flexing variable volume devices continue to demonstrate that diaphragm tissue encapsulation can be minimized by use of velour treatment of the diaphragm surface. Diffusion results, obtained primarily in long-term in vivo tests, indicate that transfer rates of high-molecular-weight ballast gases may be higher than originally predicted. Further investigation of the diffusion properties of diaphragm materials is being pursued.

A diagnostic monitoring system using signal transmission across the skin by a dipole source was developed. With this concept, diagnostic signals from permanent implanted source electrodes are picked up by surface electrodes placed on the skin, similar to electrocardiograph monitoring. All aspects of this diagnostic monitoring system have been confirmed in both in vitro and in vivo tests.

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Other key activities this last year involved development of the hybrid version of the main E3C power supply and controller circuit. Fabrication of the hybrid is now near completion, and checkout will begin soon. Also, in vitro endurance tests were continued, with the longest running system (an early E2 configuration) surpassing 4.7 years of operation without failure. One E3C-1 system was placed on in vitro endurance testing.

The culmination of the development knowledge gained over the past 4 years is represented by the Nimbus/Cleveland Clinic E3C-2 system, the concept being carried forth into the next program. This program, already under way, involves extensive reliability testing of E3C-2 systems. Eighteen systems are being fabricated, 12 to be placed on in vitro testing for 2 years' duration, and 6 to be used for in vivo tests. The basic goal of the reliability program is to validate the readiness of the E3C-2 system for initial clinical application in humans.

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NOVACOR MEDICAL CORPORATION
(DEPARTMENT OF CARDIOVASCULAR SURGERY, STANFORD UNIVERSITY MEDICAL CENTER)
Development of an Implantable Left Heart Assist System
CONTRACT NUMBER: NO1-HV-02908

An implantable, permanent, ventricular assist system (VAS) suitable for long-term human use has been developed. This integrated system incorporates the balanced MK22D solenoid energy converter coupled to a Model IVA dual pusher-plate sac-type blood pump.

The MK22D is the final step in the evolution of the balanced solenoid energy converter. The solenoid consists of two identical armature structures that move symmetrically with no reaction torques, gyroscopic effects, or momentum transfer to the body. Titanium beam springs couple the armatures directly to the pump's pusher plates.

The Model IVA blood pump has a circular pump chamber with tangential valve conduits and a seamless polyether urethane sac symmetrically actuated by dual pusher plates. The trilaminar sac is composed of diffusion-controlling butyl rubber sandwiched between two Biomer layers.

The integrated pump/converter has a mass of 695 gm and an overall volume of 400 cc. It has demonstrated synchronous operation at rates to 180 bpm, output to 11 l/min, and mean aortic pressures to 160 torr.

The VAS includes a single diaphragm-type variable volume compensator with a rigid housing supporting a Dacron-velour-covered trilaminar flexing membrane.

An implantable, microprocessor-based, electronic control and power (IECP) subsystem has been designed. Using hybrid packaging and three semicustom integrated circuits, the IECP dynamically responds to a wide range of physiologic conditions and controls solenoid closure through a unique feedback servo system. Power and communications are provided by the belt skin transformer, and backup power is available from integral rechargeable NiCd batteries.

In vivo experiments were continued with the MK22D/IVA system. A successful transition was made from the bovine to the ovine, which allows long-term system evaluation in a mature animal model, with stable hemodynamics and the absence of accelerated calcification. The change in animal model has been highlighted by an ongoing experiment with a sustained pump output of 10 l/min and no evidence of inflow

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conduit (expanded PTFE) occlusion after 5 months of continuous synchronous operation.

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SAINT LOUIS UNIVERSITY SCHOOL OF MEDICINE
Clinical Application of Ventricular Assist Devices
CONTRACT NUMBER: NO1-HV-12909

From February 1982 to August 1984, a paracorporeal pneumatic-sac type ventricular assist device (VAD) designed by Pierce and Donachy[1] and produced by Thoratec* was inserted in 22 patients ages 15 to 72 (mean 52.6) years for ventricular failure refractory to drugs and intra-aortic balloon pump (IABP). Twenty patients were unable to be weaned from cardiopulmonary bypass (CPB), and 2 patients deteriorated while awaiting cardiac transplantation. Ten patients received left VAD's; five patients received right VAD's with an IABP for left ventricular support; and seven patients received both right and left VAD's. Atrial cannulation was used for VAD inflow in all cases, and repeat sternotomy was used for VAD removal. Heparin was used only during the weaning period.

Peak VAD flows ranged from 1.55 to 3.03 (mean 2.24) $l/min/m^2$, and the perfusions lasted 3 hours to 12 days. Although all 20 of the postcardiotomy patients were weaned from CPB with the VAD, 8 of them died in the operating room of severe bleeding and biventricular failure. The other 12 patients underwent VAD perfusion for 9 hours to 12 days, and 9 patients were weaned after 3 to 1[illegible] days. Seven patients, three with left VAD's, two with right VAD's, and two with biventricular assist devices (BIVAD's), are long-term survivors of 5 to 27 months. The three patients with BIVAD's who were weaned demonstrated right ventricular recovery earlier than left ventricular recovery. Biventricular failure was present in almost all patients. However, two patients with isolated left ventricular failure did well with only left VAD's and are long-term survivors. Patients with biventricular failure who received biventricular support (either right VAD with IABP or BIVAD's) had a greater chance of being weaned (5/12) and surviving (4/12) than those who received only a left VAD (1/8).

Nuclear angiographic measurements of left ventricular volume (LV vol) and ejection fraction (LVEF) were performed during asynchronous pumping and during pump off periods. With the VAD on, LV vol decreased, but mean aortic pressure decreased and LVEF decreased. Thus, the reduction of preload was offset by an increased afterload, so that minimal LV decompression occurred. Although preoperative ventricular function did not correlate with outcome, perioperative myocardial infarction occurred much more commonly in postcardiotomy nonsurvivors (7/13) than in survivors (0/7).

Thrombus occurred in three right VAD sacs used for 3, 5, and 12 days. This was attributed to frequent cannula clamping, which was discontinued. Subsequently, a small thrombus was noted in a left VAD sac that was used for 8 days. There was no clinical necropsy evidence to suggest embolization from the device.

*Thoratec, Inc., Berkeley, California.

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From these data, we conclude:

1. Profound right ventricle (RV) and left ventricle (LV) failure may resolve with a VAD that does not provide complete ventricular decompression.

2. Biventricular failure is common in VAD candidates.

3. When present, biventricular failure should be treated with biventricular support.

4. The injured RV recovers sooner than the injured LV.

5. Perioperative infarction is an important determinant of survival in postcardiotomy VAD patients.

6. VAD sac thrombosis is rare unless the cannulas are frequently clamped.

7. Bleeding remains a major problem in VAD patients.

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THORATEC LABORATORIES CORPORATION
Fabrication of Cardiovascular Devices
CONTRACT NUMBER: NO1-HV-92906

The primary purpose of this contract is to supply clinical quality ventricular assist devices (VAD's) to Devices and Technology Branch investigators for clinical application. Included in the devices fabricated during the past year are new VAD's, refurbished VAD's, and atrial, ventricular, and aortic cannulas of various configurations. In addition, accessories such as tool sets and electrical leads were fabricated as required.

The VAD consists of a smooth seamless pumping sac made of segmented polyurethane enclosed within a rigid polysulfone case. Two tilting disk valves control flow direction, and the pump is pneumatically actuated by an external drive console.

To date, clinical VAD's supplied from this contract have been used to support the pulmonary and/or systemic circulations for up to 2 weeks in 22 patients with severe refractory left, right, or biventricular failure after cardiac surgery. The temporary use of this VAD has allowed ventricular function in seven of these patients to improve sufficiently for subsequent device removal and hospital discharge.

David J. Farrar, Ph.D., Principal Investigator

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THE PENNSYLVANIA STATE UNIVERSITY
Left Ventricular Bypass for Myocardial Infarction
GRANT NUMBER: 5 R01 HL 13426-15

PNEUMATIC ASSIST PUMP: CLINICAL STUDIES. During the past year, our group has had the opportunity to use the left ventricular assist device (LVAD) of our design in two patients and biventricular support, with similar pumps, in one patient. Each of the three patients had been in the urgent or emergency surgical category. The first patient, 59 years old, had been in profound cardiogenic shock for 8 hours when first seen. Emergency single bypass graft and LVAD insertion was performed. The poor condition of the patient prior to operation precluded survival. The second patient (31 years old) underwent emergency mitral valve replacement. Four hours later, the patient developed low cardiac output and was returned to the operating room. Biventricular support was required. Severe pulmonary hypertension, due to multiple chronic pulmonary emboli, prevented successful circulatory support. The third patient, 62 years old, developed left heart failure after urgent mitral valve replacement and five bypass grafts, and LVAD was inserted. Adequate circulatory support was provided for a few hours. However, profound right ventricular failure, related to severe pulmonary hypertension, prevented a satisfactory outcome.

During the past several years, a blood pump of our design has been used in clinical application in five other centers around the world with a number of successful applications reported.

MOTOR ASSIST PUMP: LABORATORY STUDIES. Refinement of the cam-type assist system continues. A new single-board digital-control system has been tested in vitro and a new 150 g lighter motor designed. Eight animals have received the closed system with implanted compliance chamber; the longest survivor lived 130 days, and the mean survival time is 79 days. One animal is alive and well at 87 days (August 17, 1984). The last two experiments employed a reduced size (6" x 6" x 3/8") compliance chamber that functioned as well as the larger system.

Extensive in vitro evaluation of the smaller, lighter roller screw, drive-assist system was conducted this year. The results with this system indicate potential performance and reliability improvements over the cam system.

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In vitro testing of a portable battery system and transcutaneous energy transmission system (modified Thermedics design) suitable for use have been conducted with favorable results.

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THE PENNSYLVANIA STATE UNIVERSITY
Development and Evaluation of an Artificial Heart
GRANT NUMBER: 5 R01 HL 20356-08

Pneumatically powered artificial hearts in two sizes (110 ml stroke volume--calf model, 85 ml stroke volume--human model) are undergoing continued bench and animal evaluation. The use of filler-free silicone rubber-coated inlet (atrial) connectors has eliminated pannus formation and extended animal survival. The survival time following artificial heart replacement in calves has now been extended to 9 months. Problems limiting longer survival relate to sac calcification (most prominent in high flexion areas of the segmented polyurethane sac) and growth of the animal with inadequate blood flow per kilogram of body weight. The amount of calcification appears to be less in calves on warfarin sodium and etidronate disodium.

A cardiac transplantation program has now been initiated at the Milton S. Hershey Medical Center of the Pennsylvania State University. The pneumatic artificial heart developed by our group is suitable and appropriate for use as a "bridge" for total circulatory support in certain patients awaiting transplantation. Preparations are now being made to obtain the appropriate approvals for interim circulatory support with the artificial heart.

The cam and roller screw electric motor-driven total artificial hearts have both undergone continued in vitro testing. Each system has automatically controlled cardiac output and provided left-right balance. No implanted transducers are required since aortic pressure is derived from left systolic motor current and left atrial pressure from left pump fill time. Pump beat rate and stroke time division are both automatically adjusted to maintain physiological pressures and flows.

The cam system has been implanted in five chronic animals. The last three calves lived 222, 33, and 63 days respectively. The 222-day calf, "E.T.," was automatically controlled without adjustment for the entire experiment. The next calf lived 33 days and was in excellent health when a Pyrolyte disk of a Bjork-Shiley convexo-concave valve fractured, thus terminating the experiment. We have since returned to using Delrin Bjork-Shiley convexo-concave valves, which have never failed in any of our pumps. The last animal survived 63 days and was terminated when the head of a cam follower shaft fractured and locked the rotor.

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The last two animals utilized a sealed system with a small (6" x 4" x 3/8") implanted compliance chamber. The chamber functioned well and did not affect control, although one chamber did lose gas.

In vivo studies with the roller screw are planned for the near future.

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CLEVELAND CLINIC FOUNDATION
Biventricular Assist and Replacement Studies
GRANT NUMBER: 5 R01 HL 24286-06

The long-range objective of this grant is to identify the simplest (and hence most reliable) approach for controlling a dual pusher-plate-type total artificial heart (TAH) that will at the same time respond adequately to submaximal exercise demands. Any method that depends on the explicit measurement of physiological variables (pressures, flows) has been eliminated in favor of algorithms that utilize the pump characteristics to indicate hemodynamic status. Within this subset, the choices reduce to either the two ventricles operating at variable (but independent (IND) rates) or else the rate of one slaved to the rate of the other, beating either synchronously, left master synchronus (LMS), or alternately, left master alternate (LMA). The approach for solving the problem has been to implement each of these control approaches (for 3 week intervals) on the same calf for implantation periods lasting up to 6 months. Comparisons were then made not only between algorithms on the same calf but also between calves.

Specifically, data from three calves operated in the IND mode for periods of 2 to 3 months were used as baseline information for a longer term calf (6 months and ongoing) in which the LMA, LMS, and fixed rate (FR) modes were used alternately for 3- to 4-week intervals. Toward the end of each interval, a complete battery of tests, including standard treadmill exercise (1.5 mph for 15 min), progressive exercise to obtain anaerobic thresholds (a 0.5 mph increase in speed every 3 minutes up to 3 mph maximum), drug tests (afterload increase and decrease), and volume loading, was done. Although data from this recent 191+-day calf are still being collated, results indicate the LMA mode to be at least comparable to FR and perhaps superior from the standpoint of protecting the left atrial pressure in acute situations. As in previous experiments, a left to right flow differential (averaging 10 to 15 percent) was found to exist.

Based on these data, a modified TAH has been designed, built, and tested up to 12 days in two calf experiments in which a fixed stroke volume difference (15 to 20 percent) was built into the device. Future experiments will concentrate on using this prosthesis for heavily monitored control mode studies similar to these of the previous 6+-month calf.

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PACIFIC MEDICAL CENTER, SAN FRANCISCO
Right Heart Function With Left Heart Assist
GRANT NUMBER: 5 R01 HL 27275-03

Right ventricular (RV) failure is a frequent (20 percent) complication associated with use of a left ventricular assist device (LVAD) for refractory cardiac failure after open heart surgery. Two potential detrimental effects of an LVAD on RV function are (1) reduced septal contribution to RV contraction due to left ventricular (LV) decompression and (2) augmented venous return from the LVAD, producing volume overload of an already marginal RV. There are also potential beneficial effects that include (1) the maintenance of coronary perfusion pressure and (2) reduced pulmonary pressures due to lowered LV filling pressures. Recently, we have been using ultrasonic and hemodynamic techniques to evaluate these effects and to study the interaction between LV unloading and RV function in surgical patients and laboratory animals.

The effect of LV unloading on LV and RV cross-sectional areas of patients before routine open heart surgery was examined using transesophageal two-dimensional echocardiography (TEE). LV unloading via the vent cannula prior to full bypass produced a significant decrease in LV systolic and diastolic cross-sectional areas. RV systolic and diastolic areas and pulmonary artery pressure also decreased significantly, while RV fractional area change increased over control levels, indicating an increase in ejection fraction. Data obtained from LVAD patients by TEE have shown similar decreases in LV and RV dimensions and an increase in RV fractional area change during LV assist.

In an animal model, RV and LV septum-to-free-wall dimensions were measured with ultrasonic crystals before and during LV unloading, using a pulsatile LVAD while cardiac output and heart rate were held constant. During synchronous activation of the LVAD, LV septum-to-free-wall dimensions were reduced in systole and diastole. RV dimensions, however, showed slight but significant increases that were probably due to a leftward septal shift, and RV pressure fell slightly. This implies a reduction in RV contractility because larger RV dimensions were required during LV unloading to produce the same stroke volume. The overall ability of the RV to eject a given stroke volume was not impaired because of a concomitant beneficial decrease in RV afterload during LV assist.

No evidence of RV failure was demonstrated during LV assist in any of our studies. In fact, the observed dimensional and hemodynamic effects of an LVAD imply a positive effect on the RV, especially in patients with passively elevated RV afterload secondary to increased LV filling pressures. The animal experiments, however, suggest that this effect will not be as pronounced in patients with less-diseased hearts. This hypothesis is supported by greater beneficial effects of LV unloading on RV function as previously found in patients with poor (< 55 percent)

versus relatively normal LV ejection fractions. Therefore, right heart performance will be determined by a balance between the state of the RV myocardium and the LVAD's beneficial and detrimental effects on preload, afterload, and contractility.

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UNIVERSITY OF UTAH
Physiological Control of Electric Total Artificial Hearts
GRANT NUMBER: 5 R01 HL 24338-06

This is the second year of a grant to study physiologic control of electric total artificial hearts (TAH). The overall goals of the project are: (1) to determine that an electrically powered TAH with the potential for long-term human application can maintain a growing calf in good health and (2) to identify and quantitate major physiologic requirements and engineering characteristics specific to the electric total artificial heart for human use. We are developing automatic control procedures to properly vary cardiac output with metabolic demand and to achieve balanced outputs for an electrohydraulically actuated, alternately pumped system.

We have performed 10 implantations during the past year. The first of these experiments emphasized the necessity to test the electrohydraulic heart in smaller animals. The maximum cardiac output (between 9.0 and 9.5 l/min under manual control) for the device was insufficient to handle the typical postoperative rise in venous return for the 105 kg calves we have been using. This prompted significant efforts to adapt the electrohydraulic actuator to the UTAH-100 TAH that is being developed as a pneumatic device in our laboratory. The elliptically shaped UTAH-100 heart was originally designed to achieve good fit of a 100-cc-stroke-volume heart in a small thorax. With this adaptation, we have consistently achieved excellent fit and physiologic performance in the small calf (63 to 76 kg). This major improvement has shifted our in vivo experiment problems away from difficulties in physiologic performance and implantation techniques. With the ability now to extensively test the device in vivo, we have pinpointed problems in fabrication and assembly of the device and instituted improved quality-control procedures. These developments should permit long-term testing of the device using automatic control during the upcoming final year of the grant.

In vitro studies have been in two major areas:

1. Further in vitro efforts with automatic control have demonstrated that it is possible to adjust control parameters to automatically yield a very sensitive response to right atrial pressure (RAP). Tests showed that over the 0 to 5 mm Hg RAP range, the cardiac output increased from 4.8 to 8.7 l/min and that 9.7 l/min could be achieved without exceeding 15 mm Hg RAP.

2. In vitro studies with a passively controlled compliance chamber indicate that an alternative to our present balancing method (the

high backflow pulmonic valve) is feasible. This device would adapt well to automatic control concepts and provide the same range of control over possible variations in bronchial flow that our present balancing method achieves.

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MONTREAL GENERAL HOSPITAL
Fluid Dynamics in Transparent Natural Blood Vessels
GRANT NUMBER: 5 R01 HL 29502-03

To elucidate the possible connection between blood flow and the localization of atherosclerosis and thrombosis in large arteries of the mammalian circulation, we have studied the detailed flow patterns in the dog aorta using cinemicrographic techniques.

Isolated transparent arterial trees containing the heart and the ascending and descending aorta with their major branches were successfully prepared from dogs by fixing under physiological pressure, dehydrating with ethanol, and finally suspending in oil of wintergreen. Flow was visualized by taking 16 mm cine films of the motions of tracer polystyrene microspheres in dilute suspensions undergoing steady flow through the transparent natural vessels. In the aortic arch, it was found that complex spiral secondary flows and recirculation zones form at each branching site over a wide range of Reynolds numbers. Particles in the mainstream were deflected sideways at the flow divider and traveled laterally and some backward along the vessel wall, and then some entered the side branches, while others rejoined the mainflow in the descending aorta, after describing spiral orbits. A recirculation zone was formed in each branch adjacent to the vessel wall opposite to the flow divider. When observations were made along the axis of the aorta, it was found that, looking down the aorta, the fluid revolved in a clockwise direction. Apparently, there was only one helicoidal flow rather than the two that had been anticipated. In vessels having an imperfectly opened aortic valve, it was also observed that strong eddies form at the entrance region of the aorta slightly downstream of the aortic sinus. In the descending aorta, paired thin-layered spiral secondary flows, located symmetrically about the common median plane of main and side branches, were formed at the T-junction of the celiac, cranial-mesenteric, and right and left renal arteries.

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UNIVERSITY OF UTAH
LVAD and RVAD With Portable Electropneumatic Drive
GRANT NUMBER. 1 R01 HL 29751-01A2

Comprehensive development of implantable left and right ventricular assist devices intended for long-term application has begun. The LVAD's and RVAD's are pneumatically powered by the Utah Heart Driver or Heimes Portable Heart Driver, thus permitting assist device use away from the hospital following recovery from the implantation procedure. The assist devices are placed orthotopically within the chest with the drive lines exiting via the abdominal wall. A specially designed inflow cannula will be inserted through the atrial appendage. Assist device outflow will be pumped through a woven Dacron graft anastomosed to the corresponding great vessel. The development program includes device manufacturing and many aspects of performance evaluation.

The right and left ventricular assist devices are made from thermoplastic polyurethane. All components can be made using the vacuum-forming process. The seamless ventricular intima is made either by vacuum forming or solution casting. Although originally designed to use commercial tilting-disk prosthetic valves, the blood pumps can be easily modified to accept vacuum-formed monocusp valves manufactured in our laboratory. Use of these materials and manufacturing processes minimizes the cost and time for blood pump production.

The LVAD's and RVAD's will be evaluated by durability testing, pumping performance characterization, and in vivo implantation. Durability testing includes pumping of air diaphragms and assist devices without valves in pressurized chambers. Complete assist devices are also continuously pumped on simple mock circulation systems. Pumping performance analysis will be made with a mock circulation instrumented to measure blood pump pressures and flows as the ventricular assist device pumps by itself or in parallel with a normal or failing artificial ventricle. Animal implant studies will evaluate the LVAD's and RVAD's during single and biventricular support of normal and failing sheep hearts. Some studies will be long-term survival while others will have device removal several weeks after implantation. All experimental animals will undergo rigorous hemodynamic and hematologic evaluation before, during, and after ventricular assist device application.

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CLEVELAND CLINIC FOUNDATION
Compliance System for Implantable Blood Pumps
GRANT NUMBER: 5 R01 HL 30426-02

Every pulsatile blood pump has a volume change behind the diaphragm or pusher plate equal to that on the blood side of the diaphragm. With the integration of implantable electrical and thermal drive systems with blood pumps, methods to accommodate this variable volume must be developed.

A gas-filled intrathoracic compliance chamber is a simple and practical solution to the variable volume problem. The prerequisites for this system to work properly are (1) biological compatibility that would allow stable and acceptable pressure-volume characteristics for long duration, and (2) retention of the gas mixture in an environment in which gas diffusion gradients inherently exist.

As previously reported, lenticular shaped, Dacron-velour-covered polyurethane compliance chambers showed stable, thin compliant tissue capsule formation in calves in durations of up to 2 years. These good results were reproduced in experiments in which the polyurethane membrane was replaced by Hexsyn, which offered fabrication advantages. In addition, dynamic testing showed that energy consumption due to inflation and deflation work was quite low at volume flow rates over the range 180 to 500 ml/sec. Therefore, the biological compatibility can be considered well established.

Permeability testing showed that sulfur hexafluoride (SF_6), a nontoxic, medically used gas, would have slow permeation rates and serve well as a buffer gas in the compliance gas mixture. In vivo experiments currently under way are being used to quantify the concentrations of the physiologic gases for equilibrium conditions in a closed system and gas diffusion rates. For these studies, sealed nonfunctioning compliance chambers are implanted in the thorax of calves. Chambers that were initially air filled show faster rates of volume loss than chambers initially filled with the SF_6-buffered gas mixture.

Integrated blood pump-compliance chamber in vivo experiments were initiated in which the systems were implanted as a sealed unit without external pressure or sample taps. Compliance gas volume is monitored by a Hall-effect sensor on the compliance chamber. These experiments are demonstrating that buffer gas diffusion, although relatively low, is substantial enough to necessitate some gas addition for long-term

implants. Accordingly, we are now studying buffer gas makeup methods, including constant rate as well automatic on-demand types.

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UTAH BIOMEDICAL TEST LABORATORY, INC. (UBTL)
Myocardial Recovery After Acute Ischemic Heart Failure
GRANT NUMBER: 1 R01 HL 33805-01

We have previously demonstrated that prolonged ventricular fibrillation in the extracorporeally supported sheep will result in severe subendocardial damage and a total loss of pumping ability (the "stunned myocardium"). This model for acute ischemic heart failure when supported with biventricular bypass results in eventual recovery and restoration of tolerable cardiac hemodynamics.

We are presently developing techniques to correlate myocardial metabolism with hemodynamic function during the injury period and the transition to recovery. Current efforts in the first month of this research grant have resulted in the development of myocardial biopsy techniques, delineation of pathologic and biochemical methodologies, improvements in our biventricular support system, and cardiac function monitoring.

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THERMEDICS, INC., AND CHILDREN'S HOSPITAL MEDICAL CENTER
Device Readiness Testing of Implantable Ventricular Assist Systems
CONTRACT NUMBER: N01-HV-48070

The objective of this program is the establishment of the reliability and operating characteristics of the Thermedics ventricular assist system. The data generated as a result of this program will be used to support an application for an investigational devices exemption. The system to be tested will be based around the Thermedics MK-IV energy converter. This converter is powered by a low-speed torque motor, has a minimum of moving parts, and is assembled as an integrated unit with the Thermedics model 14 pusher-plate pump. This ventricular assist device is coupled with an implantable battery pack and controller unit, a variable volume device, and a transcutaneous energy transmission system to create a totally implantable ventricular assist system that requires no penetration of the skin. An external battery pack and electronic components are also part of the system.

This program is now in the first stage. Primary emphasis has been on development of suitable test protocols and the establishment of manufacturing and acceptance specifications. Development of test protocols is a cooperative effort between the contractors involved in the project, the program office, and an independent review board. These protocols will apply to all in vitro and in vivo characterization and reliability testing.

Manufacturing and acceptance specifications are being established such that the devices will be fabricated in accordance with good manufacturing practice. Manufacture of the devices has begun.

Warren Clay, Principal Investigator
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ABIOMED (APPLIED BIOMEDICAL CORPORATION)
MASSACHUSETTS GENERAL HOSPITAL
CHARLES STARK DRAPER LABORATORY
Device Readiness Testing of an Electrohydraulic Ventricular Assist System
CONTRACT NUMBER: NO1-HV-48073

The overall objective of this 3-year program is the demonstration of the clinical readiness of an implantable electrohydraulic ventricular assist system (VAS). Potential recipients of such a permanent device are patients with end-stage ischemic or idiopathic cardiomyopathy.

During the past 4 years, the Abiomed VAS progressed from the conceptual stage to a final prototype with demonstrated effectiveness, both in vitro and in vivo. During the next 3 years, a number of systems will be fabricated and subjected to continuous in vitro reliability testing under simulated physiological conditions with the specific goal of attaining a 2-year operational lifetime. Concurrently, studies will be performed to achieve 25 animal-months of in vivo experience with a mean duration of approximately 5 months.

The system to be tested consists of (1) a dual-chambered, seamless blood pump with trileaflet valves, fabricated using Angioflex, a polyether urethane, as the blood-contacting material; (2) an electrohydraulic energy converter encased in titanium housing with an axial flow pump and a fluid-shuttling two-position, four-way sleeve valve; (3) an internal rechargeable 10-cell NiCd battery pack with an operational capacity of 30 minutes; (4) an internal electronic controller based on RCA 1805-A microprocessor; (5) an external monitor pack; (6) a rechargeable external AgZn power pack capable of 10-hour operation; and (7) a Thermedics transcutaneous energy transmission device.

During the first year of this program, 16 to 20 complete devices will be fabricated according to defined protocols. Twelve systems will be used in the reliability testing; at least four of the remaining systems will be used for animal experiments. All subcomponents and subsystems will undergo quality control, quality assurance, and acceptance testing to select qualified components for assembly. All assembled systems will be subjected to a burn-in period to weed out system infant mortality prior to the initiation of life-testing implantation. Identical systems will be used in the in vitro testing and in vivo implants, without the use of substitution components. Percutaneous connections will be used until experience is gained on the transcutaneous system.

Anatomic fit studies will be conducted on cadavers to determine device placement and orientation, organ and tissue compression effects, anastomotic site, and apical insertion technique.

In vitro reliability testing will be initiated approximately 9 to 12 months into the program and will continue for 2 years. Chronic experiments are scheduled to start in the second year. Prior to reliability testing and in vivo studies, each qualified system will undergo an extensive in vitro characterization with and without a mock loop to map out its steady state characteristics and transient response. A range of filling and outflow pressures with the associated flows and power consumption will be documented. System tracking of conditional changes, such as beat rate, synchronization, filling, and outflow pressure changes will be recorded. This set of data will serve as a reference for in vitro evaluation to determine performance changes subsequent to device explant or at the end of the reliability test period.

Reliability testing will be performed in a temperature-controlled (37° C) saline loop and bath, with a common inflow plenum and adjustable filling pressure, up to a maximum of 20 mm Hg. Each device outflow pressure is set through adjustable fluid level column height. Flow is monitored using a venturi. Filling and outflow pressures and flow and device power consumption are monitored once per hour. In addition to scheduled sampling, threshold level detectors are used to initiate data monitoring and recording in the event a device flow falls below the predefined level of 4 l/min, the NHLBI criterion for system failure.

Chronic experiments will be divided into two groups, each operating respectively in the copulsating or the counterpulsating mode. The Abiomed system lends itself to operation in both of these modes. The rationale is to determine whether long-term physiological or pathological differences exist for the two different modes of operation.

Acute in vivo system characterization will be performed during the early phase of the program in both the single and the biventricular assist modes. With minor change in the configuration, the system can provide support to both ventricles with no change in the drive and

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control unit or the system size and weight. This mode of operation can address the patient population in which chronic single ventricular support may not be sufficient.

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Ultrasound B-Scan Assessment Program

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RESEARCH TRIANGLE INSTITUTE
Data Coordinating Center for the Ultrasound B-Scan Imaging Assessment Program
CONTRACT NUMBER: N01-HV-12917

The Ultrasound B-Scan Imaging Assessment Program has consisted of a planning phase, a pilot study, and a main study and is currently in the process of a followup study. The purpose of the work is to assess the capabilities of ultrasound B-scan in imaging atherosclerotic lesions in carotid and iliofemoral arteries. B-scan is compared with results of angiography and with pathology of endarterectomy specimens. In addition to the intertechnique evaluation of the capability of B-scan for detection and quantification of atherosclerotic lesions, an intratechnique evaluation of the repeatability and variability of each of the techniques, B-scan, angiography, and pathology, has been undertaken. During the course of the main program, which ended enrollment as of the end of March 1984, over 1,200 individuals were enrolled. Of these, approximately 1,100 were entered into the intermodality evaluation and the remainder (randomly selected) into the intramodality study.

Preliminary results indicate that dimensions as measured by B-scan tend to be somewhat larger (e.g., 0.5 mm for the minimum residual lumen) than those measured by angiography. However, the coefficient of variation for the two techniques as determined by intramodality analysis of repeatability and variability are of the same order of magnitude. Intermodality comparisons of B-scan as compared with angiography indicate a 95-percent sensitivity for detection of severe carotid artery disease and an 81-percent sensitivity for detection of mild to moderate disease. The overall sensitivity of B-scan as compared with angiography is 87 percent.

Analyses of the final data base, including comparisons of B-scan, angiography, and pathology, continue.

Fred A. Bryan, Jr., Ph.D., Project Director
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THOMAS JEFFERSON UNIVERSITY HOSPITAL
Ultrasound B-Scan Assessment Program
CONTRACT NUMBER: NO1-HV-12912

In April 1981, the Division of Ultrasound and Radiologic Imaging, Thomas Jefferson University and Medical College, and four other medical facilities received a 3-year contract from the National Heart, Lung and Blood Institute of the National Institutes of Health to determine the efficacy of B-scan imaging in the detection of atherosclerotic plaques in both the carotid and lower extremity arteries. Patients participating in the B-scan study had completed recent arteriographic studies of the carotid and lower extremity arteries. Staff physicians from the Division of Ultrasound and the Department of Radiology examined the respective studies and completed protocol sheets in a double-blind study. The data sheets were designed so that measurements of the plaque that produced the minimal residual lumen of the carotid arteries were accurately calculated. The cases were read for reliability and variability or for specificity and sensitivity. The completed protocol sheets and the completed sheets for physical examination, medical history, and functional studies were forwarded to the Research Trial Institute for statistical analysis. Any specimen retrieved in an intact state during a carotid endarterectomy was processed by the pathologist according to protocol to confirm these findings.

Similarly, the arteries of the lower extremity were studied. However, the specimens were not studied from a pathology standpoint. Approximately 1,000 cases were evaluated during the contract period by the participating facilities. These institutions met quarterly to review any ongoing or newly encountered issues relating to the study. The personnel of Thomas Jefferson University Hospital examined 198 carotid patients and 36 lower extremity studies. The end results of this study indicate that there may be a role for B-scan ultrasonography in the diagnostic evaluation of atherosclerotic plaques of the carotid and lower extremity arteries. An extension to the initial contract was awarded in January 1983 for a followup examination of only the carotid patients. This examination, currently in operation, involves inviting patients back for a followup examination 12 to 18 months after their initial study. This will make it possible to ascertain progression or regression of atherosclerotic plaques on asymptomatic patients who have not had surgical intervention. To date, 54 patients have been enrolled in the followup study. Patient followups are being performed in a double-blind study, and all pertinent information is forwarded to the Research Triangle Institute for statistical analysis. A new contract proposal has been submitted recently for a second followup examination 36 months postinitial examination. In addition to the B-scan and its

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functional studies, a limited history and physical examination as well as a lipid profile will be carried out. This should provide full insight into the adequacy of B-scan imaging and complementary functional studies.

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Stanton N. Smullens, M.D., Coinvestigator

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Diagnostic Instrumentation

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JET PROPULSION LABORATORY, CALIFORNIA INSTITUTE OF TECHNOLOGY
Computer Enhancement of Intravenous Coronary Angiograms
GRANT NUMBER: 5 R01 HL 30010-02

Under optimum exposure conditions, coronary arteries can frequently be faintly seen on intravenous angiograms but not with sufficient clarity for diagnostic use. Computer processing methods are being developed as part of this study to improve visualization of these images. A complex combination of spatial and temporal filters initially developed to enhance the arterial shadows has been replaced by a simpler and faster single frame processing technique based on a feature-dependent high-pass filter. Results to date on both animal and human angiograms indicate that substantial improvement in image quality can be achieved by the processing algorithms but that overall quality is not yet sufficient for diagnostic use.

Robert H. Selzer, M.A., M.S., Principal Investigator
David H. Blankenhorn, M.D., Collaborating Investigator
Donald W. Crawford, M.D., Collaborating Investigator

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UNIVERSITY OF UTAH
Temporal Filtration Fluoroscopy, Tomography, and 3-D Display
GRANT NUMBER: 5 R01 HL 30001-02

Diagnostic quality digital coronary angiograms have been obtained and analyzed in comparison with simultaneously obtained cine angiograms using the Thomson CSF Broadcast 9300 video filtration device. Technical details of the method have been reported (Hardin, et al. Radiology 1984 May; 151(2):517). Analysis of comparative cine and digital stenotic segments shows only moderately good correlation, partly due to y-axis resolution problems caused by interleaved video readout. Efforts are under way to obtain progressive video readout to improve the video images, and a clinical protocol has been approved to evaluate the video highpass filtration technique using 4-4.5 French coronary catheters and dilute contrast material. Our ultimate goal is to develop a system suitable for outpatient screening.

Use of a Lexan plug model in vivo has shown that neither the digital nor the cine assessment of known stenoses is particularly accurate. In an effort to improve quantitative performance, we have designed and manufactured a coronary stenosis phantom that should allow better experimental assessment of stenoses with the resultant ability to fine tune a system for more satisfactory in vivo performance.

Work on cardiac tomography continues under the direction of Robert A. Kruger, Ph.D. (see separate abstract).

Three-dimensional display on a vibrating mirror system has been analyzed in comparison with two-dimensional display of identical phantom data. Feasibility of using this display system for viewing deblurred tomographic slices of other phantoms and in vivo tomograms is being studied.

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Robert A. Kruger, Ph.D., Coprincipal Investigator
Bruce E. Bray, M.D., Coinvestigator
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William H. Barry, M.D., Coinvestigator
Brent S. Baxter, Ph.D., Coinvestigator

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UNIVERSITY OF IOWA
Image Processing of Coronary Arteriograms
GRANT NUMBER: 5 RO1 HL 29976-02

We have shown that the estimation of the severity of coronary atherosclerotic stenosis by the assessment of percent diameter reduction is a poor predictor of the physiological significance of the coronary lesion. One of the major goals of our research on this grant is to develop and test methods of analysis of standard coronary arteriograms that will more accurately predict the functional significance of individual coronary lesions in humans. We previously reported that computer-assisted videodensitometry (VID) yields information that correlates with the minimal cross-sectional area of the stenotic coronary lumen and that also correlates with the physiological significance of the coronary lesion.

In the present study, we examined two methods of VID background subtraction, evaluated the reproducibility of VID, and compared the results of VID with independent geometric and physiological variables. To accomplish these goals, two sequential cineangiographic frames of proximal left anterior descending coronary arteries from 17 patients were digitized. Normal and diseased segments and adjacent background regions were chosen by two observers in each angiographic frame. Background subtraction was accomplished using two different procedures. Integrated gray level (GL) and optical density (OD) of the narrowest part of the coronary artery were then determined. The GL and OD of each lesion, as well as the percent stenosis (estimated from the digitized images), were each compared with the minimal lumen area obtained by quantitative coronary angiography (QCA) and with a measure of the functional significance of the coronary obstruction. Functional significance of each obstruction was measured by intraoperative Doppler reactive hyperemia studies of the peak-to-resting velocity ratio (PRVR) after a 20-second left anterior descending coronary occlusion.

Results:

	% Stenosis	OD	GL
PRVR	r = -0.24	r = 0.78	r = 0.79
QCA	r = -0.43	r = 0.82	r = 0.80

The particular method of background subtraction did not affect the results of our experiment. Reproducibility of VID analysis from frame to frame was excellent (r = 0.90 for OD; r = 0.96 for GL), and inter-observer reproducibility was also good (r = 0.87 for OD; r = 0.89 for GL). Estimation of percent stenosis did not correlate well with QCA or PRVR. Thus, computer-assisted videodensitometry of coronary lesions allows rapid and accurate estimation of lesion geometry and functional significance.

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We are currently continuing our investigations with coronary videodensitometry and other computer analytic methods in the analysis of coronary arteriograms of humans.

Melvin L. Marcus, M.D., Principal Investigator
David J. Skorton, M.D., Coprincipal Investigator
Steve M. Collins, Ph.D., Coinvestigator
David G. Harrison, M.D., Coinvestigator
Carl W. White, M.D., Coinvestigator
Loren F. Hiratzka, M.D., Coinvestigator

(Maryl R. Johnson, M.D., is now a coinvestigator on this project. Elizabeth E. Ericksen, M.S.E.E., Steven R. Fleagle, B.S.E.E., and Philip Aylward, M.D., were collaborators on this particular experiment.)

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UNIVERSITY OF PENNSYLVANIA
Visualization of Coronary Arteries and Bypass Grafts
GRANT NUMBER: 5 R01 HL 29985-02

We are applying technologies that have arisen in computer science and psychophysics to the improvement and evaluation of clinical performance as related to coronary arteries and coronary bypass grafts. Specifically, we are investigating how images from intravenous digital subtraction angiography (DSA) and from digital subtraction root arteriography can be enhanced and comparing the efficacy for lesion detection and quantitation of the enhanced images with unenhanced images and with those obtained by selective coronary arteriography. The enhancement techniques include the use of standard image processing methods and specifically developed techniques for vessel detection, three-dimensional blood-vessel reconstruction, modeling or myocardial dynamics, medial line representation, lumen size estimation, and display of vessel structure. Our theoretical ideas are being implemented into working software packages that will be evaluated by the techniques of receiver operating characteristic analysis applied to observer performance tests on images from a swine coronary atherosclerosis model.

Specifically, during the second year of this 3-year grant, we have developed a package for automatic measurement of coronary vessels from digital angiograms and a mathematical model for computer generating masks for an arbitrary combination of cardiac and respiratory phases. A program appropriate for nonstationary histogram equalization of DSA images has been developed, implemented, and tested. The process of artificially inducing coronary arterial disease in swine has begun, and such swine have been imaged. Equipment has been built and tested to monitor and record the respiratory and cardiac cycles and to correlate them to the imaging process.

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BOWMAN GRAY SCHOOL OF MEDICINE
Research, Development, and Evaluation of Systems for Noninvasive Detection and Quantification of Atherosclerotic Lesions
CONTRACT NUMBER: NO1-HV-12902

The detection and quantification of early atherosclerosis can be accomplished by measuring the arterial distensibility and wall thickness changes. As wall thickness increases, the arterial distensibility decreases and the pressure-strain elastic modulus increases. Arterial distensibility is defined as the systolic diameter minus the diastolic diameter divided by the diastolic diameter, and the pressure strain elastic modulus is the pulse pressure divided by the distensibility.

The research approach included a nonhuman primate model, development of deconvolution procedures to improve axial resolution, and control of the transducer output pulse. The primate colony consisted of 18 adult male Macaca fascicularis monkeys divided into three groups. Group I (seven monkeys) was fed an atherogenic diet high in butter, group II (seven monkeys) was fed an atherogenic diet high in peanut oil, and group III (four monkeys) was fed monkey chow as controls. Group I animals developed a mean plasma cholesterol concentration of 607 $\pm$ 19(SD) mg/dl, group II a mean plasma cholesterol concentration of 435 $\pm$ 106 mg/dl, and group III a mean plasma cholesterol concentration of 118 $\pm$ 13 mg/dl. These animals were sacrificed, and the results of histology will be presented.

To detect small changes in primate and human arterial wall thickness, deconvolution algorithms using the procedure of Papoulis and Chamzas were developed. Additions to this algorithm included tissue-frequency-dependent attenuation compensation and a variable threshold. Deconvolution results from young healthy human common carotid artery echoes showed two distinct echo spikes. Results from echoes in patients with known atherosclerosis and participating in an exercise rehabiiitation program showed layers in the 0.050 to 0.120 mm range.

Efforts to control the transducer output pulse were done with the EDO Corporation and later with NAMLAK. The procedure uses system identification algorithms to obtain a narrow output pulse. Results to date show a pulse with a main time lobe width of 200 ns and time sidelobes greater than 15 dB down. Axial resolution at 200 ns corresponds to 0.077 mm.

Ralph W. Barnes, Ph.D., Principal Investigator
M. Gene Bond, Ph.D., Investigator
David W. Griffith, Jr., Ph.D., Investigator
Ward A. Riley, Jr., Ph.D., Investigator

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UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
NMR Imaging of Human Coronary Arteries
CONTRACT NUMBER: NO1-HV-38044

Nuclear magnetic resonance (NMR) imaging has clearly become established as a diagnostic clinical modality, and it is certain to become widely available. A major attraction of the technique is its totally noninvasive nature and the apparent lack of hazards for devices operated below Food and Drug Administration guidelines. This noninvasiveness extends to the visualization of vasculature, which becomes evident because the process leading to image formation by NMR is slow (the time scale being from 10 msec to 1 sec) compared with flow processes.

In this program, we address techniques for imaging the coronary arteries and for the display of vasculature. The NMR imaging process consists of the application of short signal-generating sequences at preset time intervals. The image is formed from a multiple set of such sequences, from 100 to 4,000. The interval between sequences can be governed by a trigger signal obtained from the heart, in this way becoming synchronized to the cardiac cycle. If desired, imaging can be stopped during certain phases of the respiratory cycle, but this capability has not been found necessary. As part of this work, we have developed a package of cardiac imaging options that includes:

1. Five-section, double-spin echo imaging in approximately 7 minutes.

2. Ten-section single echo imaging in 7 minutes.

3. Five- or ten-section imaging showing each section at five points in the cardiac cycle in 35 minutes (cycled multisection).

4. Fifteen-section imaging at one point in the cardiac cycle in 68 minutes, with a capability of section thickness as small as 1.8 mm. Regular thickness for all modes is 7 mm. Currently, spatial resolution in these sequences is 1.7 mm and is in the process of being doubled to 0.8 mm.

Regular section thickness imaging of 127 patients and volunteers has shown the coronary arteries depicted as low-intensity structures as follows: Right coronary artery (RCA)--seen on cross-section in 78.6 percent of subjects and origin of RCA seen in 50 percent of subjects; left coronary artery (LCA)--origin seen in 55 percent of subjects and bifurcation of LCA seen in 12.8 percent; left anterior descending coronary artery--seen either in cross-section or longitudinally in 48.6 percent of subjects; left circumflex artery seen in 23.6 percent of subjects.

Thin-section imaging of the heart in five volunteers shows comparable results. The thin sections present advantages (less partial volume averaging) offset by disadvantages: for vessels crossing from one

section to another at a shallow angle, visualization through the various sections is difficult because each section contains a small portion of the vessel.

Further experimentation with intermediate thickness sections may be needed to optimize coronary artery imaging.

The second major component of this project involves the development of algorithms for reconstruction of vasculature in three dimensions, starting from a single set of tomographic images. Most of the work has been done in the abdomen. The algorithm identifies vessels by their characteristic NMR signature and determines the patent area and depth in the body of each vessel. Connections and bifurcations are searched for to establish contiguity of different vessels.

Vessels can be then displayed from any direction, with gray-scale intensity or color-coding depth. Vessel systems can be separated and displayed independently. The display can show the width of the vessel as it projects onto the viewing plane or can show the diameter corresponding to a circular cross-section of the vessel, i.e., the image encodes true patent area. Also, patent area can be color coded on the vessel. Vessel systems or individual vessels can be separated by color. Using this algorithm, we are currently in the process of comparing the clinical efficacy of NMR and angiography in 15 patients. We have also started work to extend the process to the thorax and neck.

In conclusion, NMR imaging shows promise as a noninvasive modality for visualization of the coronary arteries and may eventually be useful for assessment of proximal occlusive coronary artery disease. NMR imaging is also certain to replace large vessel angiography in many applications.

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MAYO FOUNDATION
Quantification of Coronary Artery Stenosis With the DSR
CONTRACT NUMBER: NO1-HV-38042

The main feature of this contract is the replacement of the current image isocon-based image chains with charged-coupled diode-based (CCD) image chains. Preliminary evaluations of an Oldelft NA 0.48 objective lens and a microchannel-plate-based image intensifier coupled via tapered fiberoptics to a CCD television camera show that the new image-chain characteristics meet the theoretical needs for intravenous coronary arteriography. The objective lens delivers five times more light photons to the first photo electric surface (intensifier), and the intensifier/tapered fiberoptic bundle system delivers an adequate intensity of light to the CCD television camera to permit full use of its intrascene dynamic range. The CCD camera sensor will be cooled with a thermoelectric cooling chip to around 0° C so as to ensure 1,000:1 intrascene dynamic range in the video data.

In addition to the replacement of the image chains, we are developing and implementing specially adapted reconstruction algorithms that overcome some of the artifacts caused by limited number and range of angles of view. This will be particularly important if patients have irregular heart rates during a scan, thereby reducing the effectiveness of gated reconstructions.

The main attractions to a tomographic method for imaging coronary arteries following a right-sided injection of contrast medium are that the problem of superposition is eliminated and that all angles of view are available from a single injection of contrast agent. This was demonstrated with a specially fabricated radiological phantom, which is a very life-like chest. The ribs and spine are from a 75 kg male, the heart and lungs are porcine, and the chest wall and upper abdominal contents are made of "dry" water. The left heart chambers, aorta, and coronary arteries contain approximately 1:10 diluted contrast agent so as to simulate the levophase from a right-sided injection of contrast agent. A 3 mm tract allows a catheter to be advanced via the superior vena cava, right atrium, right ventricle, and right ventricular outflow tract. The 2 mm lumen of this catheter can be modified with "stenoses" of different lengths and severity and the lumen filled with contrast agent diluted to any desired level. Scans of this phantom with the currently configured dynamic spatial reconstructor demonstrate the power of the tomography-based technique.

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STANFORD UNIVERSITY
(HANSEN LABORATORIES OF PHYSICS AND SCHOOL OF MEDICINE)
K-Edge Subtraction Angiography With Synchrotron X-Rays
CONTRACT NUMBER: NO1-HV-38039
GRANT NUMBER: 5 RO1 HL 29824-02

The purpose of this program is to conduct an evaluation of tunable synchrotron x-ray beams for use in K-edge digital subtraction angiography of coronary arteries in humans. Activity in the first year has centered on an expansion of the x-ray beam line and of the imaging apparatus to accommodate human subjects.

Detailed engineering studies of the modifications required to a wiggler-illuminated x-ray beam at the Stanford Synchrotron Radiation Laboratory (SSRL) to increase the angular width from 0.75 to 4.6 mr began in December 1983. Delivery of the wide beam (12.5 cm in the initial operating location) at full intensity is expected in January 1985. A design concept for a fast-switching x-ray monochromator of matching width has been developed, and completion of fabrication is expected by November 1984. A minimum line-exposure cycle time of 2 ms is specified for this device. The design of a room, 5 m x 3 m x 2.7 m, for angiography studies is complete, and room assembly at SSRL is expected in September 1984. An operating procedure to provide for patient safety has been developed.

Expansion of the imaging apparatus includes the fabrication of a multichannel Si(Li) x-ray detector 15 cm in width (300 channels), the provision of the associated electronic amplifiers and digitizers, the upgrading of the data acquisition and display system to record and process human subject images in real time, and the design and fabrication of a patient-positioning and scanning apparatus, or chair. Completion of all these items is expected on a schedule that will permit the efficient test and evaluation of the new imaging apparatus immediately following the commissioning of the new x-ray beam.

In vivo canine studies with the previous 2 cm wide beam were continued in the period March 13 to April 2, 1984, at a scan speed (line exposure cycle time of 8 ms) twice that used previously. The suppression of electronic image noise by a method of line-frequency synchronization proved to be very effective. These intravenous studies, mostly in the lateral project, employed power injection, R-wave triggering, and, for some animals, the suspension of respiration. Also, for some animals, reference aortic root studies were performed.

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Instrumentation studies were also conducted to demonstrate the dependence of image quality on the spacing between the energies of the two x-ray beams and to define the level of veiling-glare due to x-ray scatter in the Si(Li) detector.

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UNIVERSITY OF PITTSBURGH
Development and Evaluation of Minimally Invasive Systems for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries in Humans
CONTRACT NUMBER: NO1-HV-38041

Research, development, and clinical evaluation of an improved high-speed system of diode array digital radiography is proposed to achieve a minimally invasive detection and quantification of atherosclerotic lesions in human coronary arteries. This proposed method is based on an approach whose feasibility was demonstrated at the University of Pittsburgh under contract to the National Heart, Lung, and Blood Institute. A more advanced system is now proposed that involves the use of two parallel x-ray beams produced by a dual focal spot tube illuminating two narrow phosphor screens fiberoptically coupled to self-scanning diode arrays. The output of the diode arrays is sent to a digital computer for processing and display of digital radiographic images of blood vessels containing small amounts of iodinated contrast media as produced in an intravenous injection. As in the earlier prototype, the x-rays are collimated to form thin, fan-shaped beams that allow highly efficient rejection of scattered x-rays, thereby maximizing the ability to detect the small amount of contrast media that is found in the intravenously filled coronary arteries. Our digital technique has already allowed us to produce high resolution images of the rapidly moving coronary arteries from an intra-aortic injection of contrast material, demonstrating the potential of the digital diode technique, which arrests the motion due to the millisecond line-by-line exposure. We have also succeeded in visualizing portions of the coronary arteries with an intravenous injection using our technique, but the effects of overlying pulmonary vessels and ventricles prevented us from seeing the entire length of the arteries. In the present proposed system, the use of two closely spaced x-ray beams and solid state detection systems will allow us to use precision motion subtraction of images. The advantage provided by the use of two closely spaced detectors is that two images can be produced in the same heart cycle that are recorded 150 ms apart, allowing one to remove the fixed structures and vessels in the lung but not degrading the coronary arteries. This is because in the short time between the two images, the coronary arteries move, but the pulmonary vessels remain stationary.

During the past year, research, development, and construction of the dual beam diode array digital radiography system have been undertaken. This system will enable the recording and display of subtracted digital intravenous coronary artery images with 1,024 x 1,024 pixels over our wide bandwidth television monitor. As part of this research, the U-arm assembly of the x-ray table is being interfaced to a small computer

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enabling images to be taken with the patient stationary and the apparatus moving, which should further improve the quality of the images.

Donald Sashin, Ph.D., Principal Investigator
Klaus M. Bron, M.D., Coprincipal Investigator

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ARIZONA HEALTH SCIENCES CENTER, UNIVERSITY OF ARIZONA
Research, Development, and Evaluation of Minimally Invasive Systems for Detection and Quantification of Atherosclerotic Lesions in Coronary Arteries of Humans
CONTRACT NUMBER: NO1-HV-38046

This paper analyzes the factors involved in the noninvasive quantification of atherosclerosis. It is the objective of the University of Arizona imaging program to detect a 25-percent stenosis in a 2 mm diameter coronary artery. This paper identifies major problems associated with current imaging systems and procedures. They are (1) spatial resolution, (2) lob absorption of x-rays resulting in a low detector quantum efficiency, (3) low inherent contrast resulting from intravenous injection, and (4) low contrast resulting from scatter effects. Improvements are necessary and possible in each of these areas: (1) The spatial resolution can be improved by selecting an image intensifier employing proximity-type focusing; (2) the x-ray absorption can be improved by selecting a scintillator with increased thickness; (3) the contrast factor can be improved with a proximity-type image intensifier by using fiberoptic windows at the intensifier's input and output; (4) additional contrast improvement will result from an improved scatter grid or from application of airgap techniques; and (5) the inherent x-ray contrast may be improved by selecting a different injection method. This paper describes the design considerations of a 6-in proximity-focused x-ray image intensifier with an external scintillator (CsI) and six charge-coupled diodes coupled to the intensifier via fiberoptic tapers.

Theron W. Ovitt, M.D., Principal Investigator
Hans Roehrig, Ph.D., Senior Investigator

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THE UNIVERSITY OF WISCONSIN CLINICAL SCIENCE CENTER
Research, Development, and Evaluation of Systems for Noninvasive Detection and Quantification of Atherosclerotic Lesions in Peripheral and Coronary Arteries in Humans
CONTRACT NUMBER: NO1-HV-12905

The overall objective of this contract is to develop a system for intravenous digital subtraction angiography of the coronary arteries. During the first year of this 4-year program, progress has been mainly in the area of apparatus development.

A new digital video image processor has been completed and used for initial animal studies. This processor contains three $1{,}024^2$ x 12-bit memories and special purpose hardware, which is designed to easily test new imaging algorithms that can be programmed to proceed in real time. The system is interfaced to a digital disk capable of storing 30 512^2 images or 7.5 $1{,}024^2$ images per second.

In addition to electrocardiogram-gated phase-matched mask mode and high-pass filtering, which have already begun to be investigated, dual-energy imaging will be implemented during the second year. Two modes, one with closely spaced ECG-gated exposures and another continuous mode that provides 15 energy subtraction images per second, are planned. The latter mode has been added to our original plans based on our early impressions that continuous display is beneficial in distinguishing coronary arteries from complex background structures.

An adaptive temporal filtering algorithm has been implemented and is undergoing initial tests using computer-generated contrast-pass curves. The aim of this algorithm is to distinguish between pulmonary and coronary vessels based on the temporal history of each picture element. Several curve comparison and pixel suppression schemes will be simulated and tested using dogs.

Work on a compensating filter prepared using a computer-controlled dot-matrix printer with a cerium oxide ribbon has produced extremely encouraging results in connection with a humanoid chest phantom. We are constructing a faster multihead printer, which will be permanently mounted in an experimental chest radiography installation. Filters will also be fabricated on this device using image-intensifier data and manually positioned on our fluoroscopic apparatus to test the effects of such filters in intravenous coronary angiography.

Charles A. Mistretta, Ph.D., Principal Investigator

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STANFORD UNIVERSITY
Visualization and Quantification of Coronary Arteries Using Multiple-View Energy Subtraction Digital Radiography
CONTRACT NUMBER: NO1-HV-38045

Intravenous subtraction angiography, as currently practiced, is unable to visualize coronary arteries because of inadequate signal-to-noise ratio (SNR), motion artifacts, and obscuring intravening structures, including pulmonary vessels and heart chambers. We are studying an approach that overcomes each of these problems to enable minimally invasive visualization of these vessels. A system of digital tomosynthesis is used where a conventional digital fluoroscopy system is rotated around the patient, enabling an array of images to be acquired at different angles. Each acquisition is timed with the electrocardiogram so that the resultant vessel images will be effectively stationary. The images are combined in the computer to isolate the plane of interest containing the desired coronary arteries. Other planes are blurred, thus removing the structures of the pulmonary vessels and heart chambers. The SNR is significantly improved by the square root of the number of angular views. The soft tissue structures are removed using dual-energy acquisitions at each view.

Phantom studies have been used to determine the required number of views. Controlled bolus systems have been considered for lengthening the bolus time to accommodate sufficient views. Scatter cancellation systems have been analyzed and tested for more accurate soft tissue subtraction. Improved noise-reduction algorithms have been implemented for removing the noise penalty associated with dual-energy systems. Efficient algorithms have been studied and implemented for outlining blood vessels in poor SNR environments.

Albert Macovski, Ph.D., Principal Investigator
(W. R. Brody, Coprincipal Investigator, on leave)

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MAYO FOUNDATION
The DSR, Status Report '84
GRANT NUMBER: 5 P01 HL 04664-24

Project I--Show that in children with congenital pulmonary atresia, location and area of distribution of pulmonary perfusion by various developmental and surgical systemic to pulmonary arterial shunts can be demonstrated with a single injection of contrast medium into the root of the aorta.

Project II--Potential mismatch between lung geometry and chest wall geometry of dogs with intact chest before and after pneumothorax while maintaining the same intrathoracic air content. Results to date clearly show little change of chest wall (including diaphragm) geometry when prone but marked change in the supine animal.

Project III--Eight human volunteers were scanned awake, anesthetized, and anesthetized-paralyzed. The data suggest that reduced lung capacity during anesthesia is due primarily to movement of the diaphragm into the thoracic cavity.

Project IV--Major improvements in display of organ surfaces (e.g., endocardium or epicardium) have been developed and the algorithms optimized for rapid execution. The addition of color coding to the displays increases the information content of the display.

Project V--The varifocal mirror display system is operational. It is used to display an entire volume image, operator interactive windowing, and related manipulation of the image.

Core A--The dynamic spatial reconstructor scanner has been improved in several ways: (a) Digital encoding of scan-related information into the video scan lines--this information allows for reproducible transfer of video image sequence from videotape to videodisk; (b) this encoded record also stores the x-ray current and pulse width so that scene-to-scene dynamic range of the recorded video image by varying x-ray intensity fourfold to fivefold so as to maintain constant image intensity over the region of interest; (c) implementation of cardiac scan mode where the vertical extent of the video raster is reduced to only 11 cm of axial height, resulting in scanned slice thickness 0.9 mm in the high and 0.45 mm in lower temporal resolution scan mode.

Core B--The ModComp computer system continues to be upgraded. The implementation of the header record (see Core A) greatly facilitates ECG or pressure waveform gated reconstruction.

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Core C--The image analysis programs developed on the Cyber computer are now being implemented on Charles River System-based microprocessors. These work stations should greatly increase data analysis throughput.

Erik L. Ritman, M.D., Ph.D., Project Director
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Kai Rehder, M.D., Project Principal Investigator
Richard A. Robb, Ph.D., Project Principal Investigator
Lowell D. Harris, Ph.D., Project Principal Investigator

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BAYLOR COLLEGE OF MEDICINE
Ultrasonic Instrumentation for Cardiovascular Studies
GRANT NUMBER: 5 R01 HL 22512-07

To eliminate the need for intramyocardial transducers in measuring regional left ventricular (LV) function and to estimate the transmural distribution of LV thickening, we are developing an ultrasonic pulsed Doppler instrument that utilizes a single 10 MHz epicardial transducer. Wall thickening is evaluated by digitally integrating the velocity of myocardial layers passing back and forth through each of eight sequentially range-gated sample volumes distributed across the LV wall. The resulting displacement waveforms represent the amount of thickening between the epicardial transducer and each range gate. With the Doppler audio bandwidth extending from 1 Hz to 1 KHz, velocities from 0.08 and 80 mm/s can be processed; and using a four-quadrant zero crossing counter, resolution is 1/8 wavelength or 0.02 mm.

To determine whether there are systematic differences in endo/epi thickening over the surface of the left ventricle, we used a vacuum-attached probe mounted in a small suction cup to map the transmural distribution of LV thickening in acute dogs. With the ventricle divided into basal, central, and apical regions, our initial results in three dogs show significant differences in thickening versus depth curves. Although the total wall thickening fractions in each region are similar, thickening is uniformly distributed across the wall in the central region but is greater in the inner layers in both apical and basal regions. Thick-walled models predict that there should be more thickening in the inner layers, and on the average, our data agree. However, we do not yet have a model that predicts uniform thickening even in particular regions.

We also used the Doppler technique to study the response and recovery of inner and outer wall function in seven conscious dogs following 15 minutes of coronary occlusion and 3 days of reperfusion. We found that in general the inner wall thickens more than the outer wall and undergoes greater dysfunction with ischemia. During reperfusion, the outer wall recovers within 1 hour, but the inner wall function is still significantly depressed after 1 day, returning to control values only after 3 days.

In addition to the animal studies, we are beginning a study in patients to evaluate regional myocardial function intraoperatively using the vacuum-attached probe tested in the acute dog study. Our initial goal is to measure thickening in several regions before and after aorto-coronary artery bypass procedures. The nonrevascularized areas will

serve as controls for the effects of cardiopulmonary bypass on cardiac function. There are currently no quantitative methods for evaluating regional myocardial function in patients in an atraumatic manner.

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Mark L. Entman, M.D., Collaborating Investigator
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Robert M. Nerem, Ph.D., Collaborating Investigator
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GEORGIA INSTITUTE OF TECHNOLOGY
Hemodynamics of Normal and Diseased Carotid Arteries
GRANT NUMBER: 5 R01 HL 22635-05

The research program is designed to study flow in the normal and diseased human carotid bifurcation and to develop signal analysis techniques that allow extraction of flow field information useful in noninvasive diagnostic measurements with Doppler ultrasound. Steady and pulsatile flows in a model of the human bifurcation have been investigated using laser Doppler anemometry. These studies have delineated important differences between steady and unsteady flow behavior. Although flow separation occurred under steady conditions with a resulting region of continual low wall shear, pulsatile flow produced oscillatory wall shear during systole so that no permanent separation region existed. Flow "disturbance" included strong helical patterns and organized three dimensional configurations, particularly during the latter part of systole. However, the bifurcation model showed no turbulence over the physiological range of flow conditions studied. This phase of the work will continue with the investigation of flows in models of bifurcations that incorporate lesions. Comparisons of the model data with noninvasive velocity measurements using pulsed Doppler ultrasound in human subjects show that the features seen in the module also occur in humans.

Flow disturbance analysis methods have focused on (1) improving the determination of underlying velocity waveforms by phase shift averaging, (2) examining high-velocity disturbance through autoregressive modeling, and (3) separation of low- and high-frequency components through homomorphic filtering. We have found that the underlying velocity structure may be modeled with a fairly small number of parameters using autoregressive models. Of particular importance at low degrees of stenosis are coherent starting structures (not to be confused with coherent structures in transitional or turbulent phenomena). Also, through the homomorphic filtering method, we have been able to separate vortex-shedding phenomena from higher frequency velocity oscillations induced by vessel wall vibration.

The results to date indicate that it may be possible to characterize relatively mild degrees of stenosis using the low-frequency content of flow disturbance. Future work is to be directed toward the problems associated with geometric and flow variability, which can mask pathological disturbance.

Don P. Giddens, Ph.D., Principal Investigator
Richard I. Kitney, Ph.D., Collaborating Investigator

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BOWMAN GRAY SCHOOL OF MEDICINE
UNIVERSITY OF SOUTH CAROLINA
LOUISIANA STATE UNIVERSITY
Noninvasive Assessment of Pediatric Atherosclerosis
GRANT NUMBER: 1 R01 HL 26554-03

Previous pathological studies of atherosclerosis in an animal model (Macaca fascicularis) have demonstrated that a high cholesterol diet will produce significant preclinical coronary artery disease after a relatively short period of 18 months on the diet. An elevated systolic blood pressure was also present in these animals relative to controls. Noninvasive detection of the coronary disease was not achieved prior to necropsy.

Very early carotid artery disease was also found to be present in these animals at necropsy. While not resulting in a narrowed lumen, the disease was found to produce a significant stiffening of these arteries compared with controls. This stiffness was measured prior to necropsy using noninvasive ultrasonic techniques and standard blood pressure measurements.

Recently, similar measurements were made on the carotid arteries of a subpopulation of the Bogalusa Heart Study. Children were selected for study based on their values of the two risk factors (cholesterol and blood pressure) arising in the studies described above on M. fascicularis. A high-risk group was selected, which had values of both total serum cholesterol and systolic blood pressure in the top tertile for their sex-race group as determined in two previous screenings. The low-risk group was selected to have these parameters in the bottom tertile. The ages ranged from 10 to 16 years. Preliminary data illustrating the differences in carotid artery stiffness observed in the white population studied are given below.

Sex	Male		Female	
Risk	High	Low	High	Low
Mean Age, Years	13.3	12.9	12.8	13.3
Mean Systolic Pressure, mm Hg	114	95	115	94
Total Serum Cholesterol, mg/dl	199	124	192	130

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Arterial Stiffness, kPa (mean ± sem)	67 ± 3	61 ± 2	61 ± 3	50 ± 2

These results suggest that physiologically significant changes may already be occurring in the carotid arteries of children possessing elevated levels of adult risk factors by the beginning of the teenage years. Taken together with the earlier studies on M. fascicularis, the results suggest the potential use of this technique in identifying individuals highly susceptible to atherosclerosis at an early period of life where therapeutic intervention could be most effective.

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David Freedman, Ph.D., Collaborating Investigator
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UNIVERSITY OF IOWA
Assessment of In Vivo Passive Myocardial Stiffness
GRANT NUMBER: 2 R01 HL 27035-03

The passive elastic behavior of the myocardium is one of the factors that determines left ventricular (LV) diastolic properties and that has important implications for ventricular function in a variety of clinical circumstances. In this project, we are using a combined ultrasonic/hemodynamic technique for the reconstruction of the three-dimensional geometry of the LV and for the estimation of the myocardial elastic properties using the finite element technique. Our major goal for this grant year is to assess the changes in passive myocardial elastic properties in regions of acute ischemia induced by the occlusion of the circumflex coronary artery in an open chest canine model. Cross-sectional echocardiographic images of the canine LV are recorded with the echo transducer mounted in a specially designed articulated arm so that the relative orientation of the images is known from the readings of the six potentiometers mounted on the arm. LV pressure is measured using a high-fidelity catheter-tipped transducer. Three-dimensional LV geometry is reconstructed with the aid of a computer from 8 to 12 short-axis images. Using the data from early and late diastole, we estimate the myocardial elastic modulus using the finite element technique and an optimization algorithm. Repeating the experiment after the occlusion of the circumflex artery, our analysis technique is able to identify regions of increased elastic modulus that correlate with the distributional (risk) area of the occluded artery.

During this grant year, we also propose to apply this method to images acquired from a fast computerized tomography scanner in the animal model. This technique enables us to acquire 8 to 12 parallel images of the LV within a few consecutive cycles where the endocardial and epicardial edges are more clearly defined than those obtained with the present generation ultrasonic scanners.

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MEDICAL COLLEGE OF WISCONSIN
Noninvasive Cerebral Blood Flow Measurement
GRANT NUMBER: 5 R01 HL 27130-03

Noninvasive volumetric blood flow measurement using nuclear magnetic resonance (NMR) techniques is accomplished with continuous-wave radio-frequency excitation. For the measurement of cerebral blood flow, a 63.5 cm ID, 1.1 m long warm-air for superconducting magnet (variable from 0 to 20,000 gauss) is employed. For current studies, a magnetic field of 5,026 gauss (21.4 MHc) is used. Liquid helium is maintained in the magnet by a recycling helium liquefier. Liquid nitrogen jacket cooling is not required, and cool down of the magnet can be accomplished simply with liquefication of gaseous helium by the helium liquefier.

Two types of crossed-coil NMR detectors have been used. The first type of detector has a flat geometry and can be placed on the surface of the body to measure flow in vessels directly below it. A ranging technique was implemented, using oscillating gradient magnetic fields, to focus on specific arteries. This method enabled flow to be measured in the carotid arteries (common, internal, and external) as well as in the middle of the cerebral artery (using signal averaging techniques). A two-dimensional scanning technique, also using oscillating-gradient magnetic field, has been used to produce an image of blood flow in the carotid artery.

The second type of NMR detector has a cylindrical geometry. The transmitter and receiver coils are mounted on a plastic tube, into which the head can be inserted. This type of detector has the advantage of a nearly uniform sensitivity throughout the volume of the head. In contrast, the flat crossed-coil detector has a decreasing sensitivity both perpendicular and parallel to the surface of the skin. The cylindrical crossed-coil detector is currently being evaluated in vitro.

Joseph H. Battocletti, Ph.D., Principal Investigator
Anthony Sances, Jr., Ph.D., Coinvestigator

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UNIVERSITY OF PITTSBURGH
Local Cerebral Blood Flow by Serial CT Imaging
GRANT NUMBER: 2 RO1 HL 27208-04

We are studying the measurement of local cerebral blood flow (LCBF) by the use of computerized tomography (CT) during and after the inhalation of nonradioactive (stable) xenon gas in the baboon. The method has provided LBF information with a relatively high degree of spatial resolution and anatomical correlation.

With the computer, we calculate a blood flow value for each CT volume unit (voxel). By reference to a gray or color scale, the computer then produces blood flow maps with high resolution (fullwave, half magnitude < 5 mm), which correlate to anatomical structures. The flow information derived from these maps corresponds to the physiological condition of the subject and has equally good resolution and sensitivity for superficial and deep brain regions. We simultaneously compute the partition coefficient for each unit of tissue volume in an effort to increase accuracy and the applicability of this method to diseased and abnormal tissues. The rapid multilevel CT scanning used in these studies permits examination of blood flow within multiple brain levels during a single 4- to 6-minute xenon inhalation. We have developed the ability to reconstruct from these multiple levels a display of LCBF in three dimensions in any preselected region of interest with a spatial resolution of 5 mm or better in each direction (x,y,z).

This method has been used to measure changes in LCBF that occur after pharmacologic and surgical manipulation. Blood flow maps are also able to demonstrate progressive increases in local blood flow that result from progressive elevations of $PaCO_2$ as well as regional reductions in flow that result from surgical ablation of perforating branches of the middle cerebral artery.

We have investigated the validity of the xenon technique and the effect of xenon inhalation on blood flow in studies comparing the xenon gas method and the microspheres method in the measure of LCBF, using the same tissue volumes and under similar conditions. The results of the combined data indicate that an overall association between the two methods exists ($P < 0.0005$).

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Future efforts in this project will concentrate on establishing the validity and accuracy of this method in low blood flow states.

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PENNSYLVANIA STATE UNIVERSITY
Dynamic Radiographic Assessment of Myocardial Function
GRANT NUMBER: 2 RO1 HL 27437-03

Regional wall dynamics, wall thickening, and myocardial perfusion patterns provide sensitive measures of ventricular performance and its correlation with myocardial infarction and ischemia. Nevertheless, techniques currently available for obtaining such measurements are often expensive, invasive, or of limited resolution. A new technology (dynamic radiography), based on the analysis of secondary radiation fields (scattered and fluorescence), for obtaining such data is under development.

Three-dimensional epicardial wall dynamics are measured using a seven-detector array to interrogate x-rays scattered from the epicardial surface. Real-time dynamic displays of epicardial surface contours are shown on a cathode ray tube screen. Scan times (close-chest canines) from initiation to data display are under 10 seconds. Epicardial surface location is accurate to 0.2 mm (SD) and local wall displacements to 0.1 mm (SD). Surfaces behind or in front of the cardiac silhouette are located with equal accuracy.

Wall thickness measurements are accomplished with a two-detector array. Radiation scatter is used to measure epicardial dynamics, and x-ray-induced fluorescence from the blood pool-myocardium interface is used to measure the dynamics of the endocardium. A prototype has been tested on mechanical models and experimental animals (dogs). Measurements of epicardial and endocardial wall excursions and percent wall thickening agree with the results of others.

Myocardial perfusion measurements are also obtained with a two-detector system. A sodium iodide detector monitoring x-ray scatter from the epicardial surface is used to guide a germanium spectrometer such that its collimated field of view is restricted to tissue locations on the myocardial free wall. Iodine fluorescence measurements are made subsequent to an intravenous injection of contrast agent. Measurements of local static and dynamic contrast distributions have been carried out on mechanical models, excised canine and pig hearts, and in open- and close-chest canine preparations (with and without coronary ligations) to show regional perfusion patterns.

The development of this dynamic radiographic technology should result in a combined diagnostic system capable of measuring submillimeter ventricular wall dynamics, myocardial perfusion patterns, and ventricular wall thickening. Radiation dose levels (< 250 mr) are low, and component costs (< 20K) for the current prototype systems were modest.

Joseph J. McInerney, Ph.D., Principal Investigator
Edward S. Kenney, Ph.D., Coinvestigator
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UNIVERSITY OF PENNSYLVANIA
Development and Testing of Clinical Blood Viscometer
GRANT NUMBER: 5 R01 HL 28105-02

We have completed development and are currently testing clinically a viscometer capable of measuring the shear-dependent viscosity of whole fresh blood. The device employs an unsteady capillary flow and is capable of measuring blood viscosities over shear-rate range of 1 to 1,000 inverse seconds. On any individual run, a shear-rate range on the order of 50 to 1 can be covered. Because each experiment takes on the order of 15 to 60 seconds, no anticoagulants are needed. The device incorporates a digital recording and analysis system, which can provide immediate analysis of the results and fitting of the data to different blood rheological models. Currently, Power Law and Casson model parameters are available as well as calculations of apparent viscosity at any desired shear rate. Individual samples are reproducible to better than 1 percent, with predicted parameters on repeat samples being reproducible to about 1 percent. The instrument is currently being evaluated at a number of clinical locations and with subjects from various types of studies, including (1) studies of blood viscosity parameters in stroke and in hemodilution methods for treating stroke, (2) evaluation of whole blood rheology parameters in sickle cell anemia, and (3) evaluation of whole blood rheology in peripheral vascular disease.

Mitchell Litt, D.Eng.Sc., Principal Investigator
John Seybert, Research Fellow

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UNIVERSITY OF PENNSYLVANIA
Computer Technology for Transaxial Tomography
GRANT NUMBER: 5 R01 HL 28438-04

This is a continuing project on computer technology for transaxial tomography devices. Attention is being given to reducing the required time, cost, and dose for improved reconstructions, especially from data obtained from rapidly moving objects (heart) or from large amounts of data covering the whole extent of a big organ (lungs), and to displaying the results obtained from such data in a truly effective way. This is done by improvements to an existing programming system and data base, use of optimization techniques, minicomputer implementation of an operator-interactive graphics system, and development of special purpose algorithms for reconstruction from incomplete and/or limited view projection data. Continued cooperation with clinical facilities and manufacturers of computerized transaxial tomography equipment provides immediate medical application of our work. In particular, attention is paid to the needs of such state-of-the-art developments as low-dose detection of cancer lesions, interactive surgical planning, and reconstruction and analysis of the beating heart from echocardiograms.

In particular, during the last fiscal year of the grant, we have published papers on reconstruction problems, including (1) multilevel image reconstruction, (2) entropy maximization, (3) strongly underrelaxed algebraic reconstruction techniques for inconsistent systems, (4) sparsely sampled data, (5) cone beam inversion, (6) beam-hardening correction, and (7) missing data. We have also published papers on display problems, including interactive segmentation, representation of three-dimensional data on two-dimensional display, directed contour representation, computer architecture, surface tracking, and application to craniofacial surgical planning.

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THE PENNSYLVANIA STATE UNIVERSITY
Ultrasonic Scattering by Biological Tissues
GRANT NUMBER: 5 R01 HL28425-02

This project is directed at furthering the understanding of scattering mechanisms of ultrasound in biological tissues. This understanding is crucial to the accurate interpretation of echographic appearance of tissue structures in images obtained by ultrasonic scanners.

Using a computerized experimental system that facilitates rapid data collection, attenuation coefficient, and backscattering properties, including backscatter at a single frequency (mainly at 7.5 MHz), backscatter over the frequency of 3 to 8 MHz, and integrated backscatter over the same frequency range, have been determined for various bovine tissues such as heart, liver, spleen, pancreas, and normal human blood as a function of time during coagulation. In addition, these properties have also been measured for several types of pathological bovine tissues, namely, liver abscess and cardiac tumors. Following acoustical measurements, the tissues are examined histologically.

Preliminary results indicate that, of the tissues studied, backscatter from liver is the highest while spleen has the lowest backscatter. Each tissue also exhibits a distinct frequency dependence. Backscatter from the solid portion of liver abscess was found to be significantly smaller than that of normal liver, whereas cardiac sarcoma and lymphoma typically have a backscatter less than that of normal myocardium.

Results on thrombus demonstrate that backscatter from thrombus of 12 hours is at least 18 dB higher than that of blood over this frequency range. A comparison to the backscatter of bovine myocardium shows that myocardium is more echogenic than fresh thrombus and is less echogenic than thrombus more than 12 hours old. Similar results were also obtained for integrated backscatter measurements.

Further investigations into the statistical nature of echoes backscattered from these tissues reveal that amplitude distribution of echoes from liver is governed by Rayleigh statistics. On the other hand, echoes from heart and kidney are Rician distributed, indicating the presence of a coherent component in the signal.

K. Kirk Shung, Ph.D., Principal Investigator
Terry M. Wilson, D.V.M., Collaborating Investigator
John Tarbell, Ph.D., Collaborating Investigator

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UNIVERSITY OF MICHIGAN
Automatic Processing of Digital Echocardiography
GRANT NUMBER: 5 RO1 HL 29716-02

We are presently developing and implementing new methods of direct line-mode digitization of two-dimensional echocardiography (2D echo) images. The envelope-detected radio frequency signal is acquired in a digital format for further processing. We have investigated various image processing algorithms to perform time-varying edge detection. Presently, we are concentrating on an algorithm based on using gaussian filtering to smooth the image both spatially and temporally followed by a Laplacian-like operation. These new algorithms use much larger windows than the 3 x 3 windows that are typically used.

To test our directly digitized images and edge detection algorithms, we have constructed a 2D echo cardiac phantom and a computer simulation of 2D echo images of the left ventricle in the short-axis projection. The cardiac phantom consists of synthetic tissue equivalent material containing 16 eccentric annuli of different echogenicity. The inner diameters of the annuli vary from 3.0 to 4.8 cm, and the outer diameters from 6.0 to 7.1 cm. Using standard video-based 2D echo, the diameters and areas of the 2D echo measures correlated highly with actual measurements ($r = 0.99$, $r = 0.98$, respectively). There was a downward bias of these measurements, which appeared to be related to true physical beam spread and an underestimating boundary-tracing rule.

We have also created a 2D echo model of the beating heart, which has five parameters: Cardiac chamber size, epicardium eccentricity, individual contraction rates for the endocardium and epicardium, and speckle. The backscattering effect of 2D echo, often referred to as speckle noise, was created using a Monte Carlo technique to populate a 2D random-scatterer field. The scatterers were imaged by a 50 percent fractional bandwidth transducer with a position invariant, point-spread function. Analysis of the detected envelope signal demonstrated Rayleigh statistics. A standard figure of merit was used as a performance measure for all automatic boundary techniques. Time-varying edge operators had a 25 percent greater performance measure compared with classical operators.

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UNIVERSITY OF UTAH
Tomographic Digital Subtraction Angiography
GRANT NUMBER: 1 R01 HL 31984-01

While subtraction image processing removes the majority of nonopacified vasculature in angiography, annoying patient motion and vessel overlap remain the predominant sources of image degradation. Classic (focal plane) tomography is being combined with digital subtraction angiography in an effort to overcome these present deficiencies. Initial animal studies using limited angle circular tomographic image acquisition have demonstrated that both patient motion and vessel overlap are largely mitigated with the incorporation of tomographic acquisition and tomosynthetic focal plane reconstructions.

The resulting tomosynthetic subtraction images are far from optimum, however. Blurred vascular image contrast from overlying planes still can compromise the image quality. For noncardiac imaging, an iterative least squares technique (ILST), "ectomographic" image processing, and selective plane removal (SPR) are being studied to improve the present image quality. Relative performance of the three methods is being studied using circular tomographic geometry and 8 and 16 projections. In a related study, SPR image processing is being used in an effort to quantitate ventricular volumes from limited angle projection data.

A unique x-ray tube is being designed to perform circular tomographic imaging of the beating heart. The x-ray tube design incorporates a cylindrical stationary anode and stationary cathode with electronic beam steerage to produce a "moving focal spot" x-ray source that will permit the formation of focal plane tomographic images in 0.005 and 0.030 seconds. At the output of the image detector, an image intensifier, the light optics will be modified to track the projected motion of anatomy within preselected planes, thereby producing tomosynthetic images directly. A mechanical (galvanometer mirror scanner) and an electro-optical (optical image intensifier) are being studied as candidates for this tracking optical system.

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Therapeutic Instrumentation and Devices

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PENNSYLVANIA STATE UNIVERSITY
Elimination of Reoperative Cardiac Pacemaker Surgery
GRANT NUMBERS: 5R01 HL13988-12
5K04 HL00586-04

Extruded urethane tubing has largely replaced silicone as the insulation of choice on cardiac pacemaker leads. Although this urethane has been shown to be biocompatible, there have been reports of insulation defects. Our studies were on a Biomer-like segmented polyether polyurethane (SPU) that is solvent-dissolved (dimethylacetamide) and applied directly to the wire by a coextrusion process. By using this technique, small diameter, yet very strong, pacemaker leads can be made. The leads can be coated evenly and uniformly along their entire length. Because this SPU has a heat settable, memory-retaining characteristic, it is not necessary to build up extra material or have extra wire at the J-bend of atrial leads for the lead to maintain its shape and placement. The result has been the development of atrial leads of the same OD as standard ventricular leads (1.4 mm), special-purpose ventricular leads smaller than 1.0 mm, and coaxial leads less than 2.3 mm. The stiffness and handling characteristic of each lead can be modified by varying the thickness of the polymer coating over essentially an infinite range. Furthermore, because there is a physical bonding of the SPU to the wire, the strength and elasticity of the polymer is added to that of the wire coils, enabling them to flex together smoother and longer than extruded urethane-covered leads. Stress-strain analysis consistently demonstrated a 7 to 25 times greater flex life when the SPU-bonded leads were compared against identical wires covered with extruded tubing. There was no frictional wearing of this SPU polymer from the inside because the polymer and wire are bonded together and never rubbing against each other.

The results of the animal tests in rats, rabbits, and dogs for over 3 years demonstrated the long-term biocompatibility and nonthrombogenicity of this SPU. There was never any case of an adverse response in any animal. The leads remained thrombus and fibrosis-free along their entire transvenous length. Muscle and subcutaneous tissue responses were minimal. The response of the blood and vascular tissue to SPU was far less than that reported for silicone pacemaker leads. Polarizing-light microscopy failed to show any indication of stress-induced light defraction. The leads have not shown stress-related features or any sign of developing crazing or cracking, either before or after any of the in vivo or in vitro testing. The pacing-sensing functions of the SPU leads remained at levels comparable to other lead systems.

The SPU has a high modulus of elongation (> 700 percent), low creep, great strength (> 6,000 psi), memory-retaining characteristics, and great flexibility (> 100 million cycles), making this SPU an ideal insulating material for pacemaker leads as well as many other biomedical applications. Coextruding the lead with the conductive wire results in a highly compliant, stress-free conductive system for pacemakers.

Howard C. Hughes, V.M.D., M.S., Principal Investigator

UNIVERSITY OF MISSOURI
Waveform Dependency in Defibrillation
GRANT NUMBER: 5 R01 HL 18040-09

Prior studies have shown that a broad category of symmetrical and asymmetrical bidirectional rectangular wave shocks are superior to the most favorable unidirectional rectangular wave shocks in the transthoracic defibrillation of 100 kg calves. While convenient for research purposes because the various parameters can be specified easily, rectangular wave shocks are difficult to generate in clinical-sized defibrillators.

Based upon our experience with bidirectional rectangular waveforms, we are currently studying symmetrical and asymmetrical bidirectional truncated exponential wave shocks that can be implemented in clinical-sized apparatus.

In the first portion of the study, the effectiveness of waveforms in which the leading and lagging half-cycles were of equal duration was studied in 960 fibrillation-defibrillation episodes in 90 to 110 kg calves. The initial and final current amplitudes of the leading and lagging half-cycles and the total durations of the eight waveforms evaluated were respectively 70, 35, 35, 18 A-7.54 ms; 70, 35, 70, 35 A-7.54 ms; 70, 50, 35, 25 A-5.60 ms; 70, 50, 70, 50 A-5.60 ms; 70, 35, 18, 9 A-15.1 ms; 70, 35, 35, 18 A-15.1 ms; 70, 50, 18, 13 A-11.2 ms; and 70, 50, 35, 25 A-11.2 ms. These waveforms, involving delivered energy levels in the 250 to 500 joule range, yielded first-shock percent success levels of 87 through 100 percent in calves that had been fibrillating for 30 seconds. Four of the waveforms were 96 to 100 percent successful, with the 70, 50, 35, 25 A-11.2 ms waveform being 100 percent successful. The second and third portions of this study, which are currently under way (August 1984), involve initial currents of 50 and 100 amperes.

Our data support the proposition that the bidirectional truncated exponential shocks are well behaved and that their performance is predictable from that of associated bidirectional rectangular wave shocks. Although there are uncertainties in extrapolating experience from the 100 kg calf to the human, we interpret the results of this and earlier studies as warranting clinical trials of bidirectional truncated exponential wave defibrillators.

John C. Schuder, Ph.D., Principal Investigator
Harry Stoeckle, M.D., Collaborating Investigator
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NEWARK BETH ISRAEL MEDICAL CENTER
Thermal Control of Heart Rate
GRANT NUMBER: 5 RO1 HL 23527-06

Arrhythmias, particularly sinus tachycardia, are often seen after open-heart surgery or in the course of an acute myocardial infarct. Pharmacologic agents are often ineffective to control these arrhythmias or may be contraindicated. Carotid sinus pressure and various types of pacing, such as rapid atrial pacing, paired or coupled pacing, and timed extrasystoles, are often ineffective, especially in febrile states.

In the operating room during open-heart surgery, we have seen that heart rate is easily and quickly controlled by slight local temperature changes of the sinoatrial (SA) node. We have evaluated this effect initially in an animal model using an open-chest preparation. Small cooling thermodes were designed to operate in conjunction with miniature thermocouples to cool and monitor the SA node. Initial data demonstrate the feasibility for varying SA node temperature to control heart rate within a clinically useful range.

A system has been developed that utilizes a microcomputer servo-system to control the flow of refrigerated saline to the thermode. Flow rate is controlled to maintain a preselected heart rate. The system used heart rate data obtained from limb leads and is electrically isolated. Evaluation in the dog has shown it to be simple to apply and use. Clinical trials are in progress.

Victor Parsonnet, M.D., Principal Investigator
David Glass, M.D., Collaborating Investigator
Alexander Villanueva, B.Sc., Collaborating Investigator

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CASE WESTERN RESERVE UNIVERSITY
Defibrillator Waveshape Optimization
GRANT NUMBER: 5 R01 HL 24606-05

The efficacy of cardiac defibrillation can be improved by increasing the safety factor (ratio between dysfunction-inducing shock intensity and defibrillation-inducing shock intensity) of the defibrillator waveform. This can be achieved either by increasing the current producing a specific degree of postshock dysfunction or by decreasing the current producing defibrillation. Previous studies showed that biphasic waveforms having low amplitude negative portions significantly reduce postshock dysfunction, increasing safety factor.

Our studies during the past year focused on the second method of improving safety factor--lowering defibrillation threshold. The currently accepted hypothesis is that defibrillation is achieved by exciting a critical mass of tissue, rendering the tissue nonexcitable, and interrupting the circus movement. Consistent with this hypothesis, excitation thresholds for monophasic waveforms during diastole were used successfully to compare relative defibrillation thresholds (Jones et al; 1982). However, biphasic waveforms, which do not significantly alter the diastolic excitation threshold when compared with the corresponding monophasic waveform, significantly reduce defibrillation threshold (up to 60 percent of the value for the corresponding monophasic waveform, Schuder, 1983). In reconciling this apparent conflict between the defibrillation hypothesis and experimental results, we hypothesized that a conditioning hyperpolarizing prepulse might increase the efficacy of stimulation during the refractory period. To test this hypothesis, we compared the effect of monophasic and biphasic waveform stimulation during diastole and during several stages of the refractory period in cultured myocardial cells and in Purkinje fibers. During diastole, excitation thresholds were similar for monophasic and biphasic waveforms. However, during latter phases of the refractory period, the biphasic waveform significantly prolonged total refractory period when compared with the control monophasic waveform. At a stimulus interval of 275 msec, a biphasic stimulus four times diastolic threshold produced a total action potential duration that was 1.5 times the duration produced by the positive portion only. In contrast, at 175 msec, no action potential prolongation was produced by either monophasic or biphasic waveforms. These experimental results agreed with those obtained theoretically using a modified Beeler and Reuter model of the ventricular action potential.

The increased efficacy of biphasic waveforms in exciting partially refractory cells can explain in part the decreased defibrillation threshold produced by these waveforms, since the effect is greatest in those cells that could not be excited by a monophasic waveform but would then become excitable to continue the circus movement.

Janice L. Jones, Ph.D., Principal Investigator
Ronald E. Jones, M.S.E.E., Coinvestigator

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CASE WESTERN RESERVE UNIVERSITY
Defibrillator-Induced Dysfunction
GRANT NUMBER: 2 R01 HL 26924-04

Previous experiments demonstrated that postcountershock refibrillation, evidenced by a failure to defibrillate, is produced by a shock-induced, prolonged depolarization of the myocardial cell membrane lasting up to several minutes. Preliminary experiments with cultured myocardial cells suggested that this depolarization was associated with transient sarcolemmal microlesions, since 10 K molecular weight fluorescein isothiocyanate (FITC) dextrans were found intracellularly following 6-200 V/cm, 5 msec, rectangular-wave electric-field stimuli but not following 100 V/cm stimuli. Therefore, the goals of the present experiments were to confirm this finding, to determine whether 4 K dextrans were incorporated at 100 V/cm, and to define the localization of these microlesions on the membrane.

Cultured myocardial cells, placed in normal growth medium containing FITC-dextrans, fluorescent molecules to which the membrane is not normally permeable, were subjected to 6-5 ms, rectangular-wave electric-field stimuli having intensities of 0 V/cm (control), 100 V/cm, or 200 V/cm. Dextran sizes were nominally 4 K, 10 K, 20 K, 40 K, or 70 K. Ten minutes after shock, cells were rinsed and photographed (phase and fluorescence) at 40 X and 100 X (oil-immersion). The resulting photographs were examined for the presence and localization of intracellular marker.

The results demonstrated the intracellular presence of 4 K and 10 K dextrans following 200 V/cm shocks in 100 percent (4 K) and 83 percent (10 K) of photographs. Dextrans of 20 K, 40 K, and 70 K were excluded. Dextran incorporation correlated with extensive blebbing of the cell surface, with individual blebs exceeding 10 in diameter. In general, dextrans were not incorporated in cells without blebs, or in cells having only "microblebs" less than 10 . Even though the electric field was approximately uniform, dextrans were not incorporated uniformly but were found primarily in cells from groups with good preshock cell-to-cell coupling (which increases effective cell size) and in cells oriented with their long axes in the direction of the field. Following 100 V/cm shocks, 4 K dextrans were incorporated in 50 percent of photographs; 10 K dextrans or larger were not incorporated. The 4 K dextran incorporation was in cells without membrane blebs.

These results suggest a correlation between increased membrane permeability to macromolecules less than 40A (10 K), membrane blebbing, contracture, cell-to-cell uncoupling and depolarization following high intensity electric shock.

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ARZCO MEDICAL ELECTRONICS, INC.
Swallowable Electrodes for Temporary Cardiac Pacing
GRANT NUMBER: 1 R43 HL 32378-01

Temporary atrial pacing is of value in the management of several arrhythmias, in the termination of supraventricular tachycardia, for diagnosis of conduction disorders, and differentiation of mechanisms of reentry and automaticity. New applications for atrial pacing include stress testing in patients unable to exercise and elevation and/or control of heart rate during studies of ventricular function, particularly in connection with imaging procedures. Transesophageal atrial pacing offers an alternative to transvenous catheterization and, with the development of an easily swallowed pill electrode, has become a simple and noninvasive clinical procedure.

To address the unique requirements of transesophageal pacing, we have designed a stimulator that can deliver the current required for consistent capture, typically 15 to 25 mA, and the pulse widths necessary to excite remote tissue, for example, up to 10 msec. During this study, we have added two modifications to our transesophageal cardiac stimulator: a small electrocardiographic amplifier/recorder and an output waveshaping circuit. The first modification provides for locating the esophageal electrode after swallowing and for verifying capture during pacing. The second will permit the device to be used in a switched pace/sense operation.

To optimize our electrode design, we have derived an analytic solution for current densities anywhere in the heart as a function of bipolar spacing and location of the electrode. We have examined three cases of interelectrode spacing: that of the present pill electrode (nominally 1.0 cm), a 3.0 cm, and a 6.0 cm electrode. Our conclusions are that the 1.0 cm electrode remains the preferred embodiment with its excellent proximity effect and ease of encapsulation, but precise positioning is crucial. The 6.0 cm electrode displays a diffuse current density pattern with little attenuation at remote sites, posing the danger of inadvertent stimulation of the ventricle. The 3.0 cm electrode will tolerate considerable esophageal misalignment without loss of capture and offers an attractive alternative to the closely spaced electrode in clinical situations where a more forgiving electrode may be needed. Because of this feature, we have designed a special 3.0 cm electrode that can be compressed to fit within a gelatin capsule and extends upon swallowing to the correct bipolar spacing. Clinical testing will be required to evaluate the new design.

The pill electrode may replace cardiac catheterization in a variety of diagnostic and therapeutic applications resulting in outpatient procedures with greatly reduced complexity and cost.

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